

Exhibit 11

Exhibit 12

Exhibit 13

Exhibit 14

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY**

CELGENE CORPORATION,

Plaintiff,

v.

PAR PHARMACEUTICAL, INC., PAR
PHARMACEUTICAL COMPANIES, INC.,
and TEVA PHARMACEUTICALS USA,
INC.

Defendants.

C.A. No. 17-3159 (ES)(JAD)

CELGENE CORPORATION,

Plaintiff,

v.

HETERO LABS LIMITED, HETERO
LABS LIMITED UNIT-V, HETERO
DRUGS LIMITED, HETERO USA, INC.,
AUROBINDO PHARMA LIMITED,
AUROBINDO PHARMA USA, INC.,
AUROLIFE PHARMA LLC, EUGIA
PHARMA SPECIALTIES LIMITED,
APOTEX INC., APOTEX CORP., MYLAN
PHARMACEUTICALS, INC., MYLAN
INC., MYLAN, N.V., and
BRECKENRIDGE PHARMACEUTICAL,
INC.,

Defendants.

C.A. No. 17-3387 (ES) (JAD)

**DEFENDANTS' INVALIDITY CONTENTIONS WITH RESPECT
TO U.S. PATENT NOS. 8,198,262; 8,673,939; 8,735,428 AND 8,828,427**

Pursuant to the Scheduling Order (D.I. 65) and Local Patent Rules 3.3 and 3.6(c) of the District of New Jersey, Defendants Mylan Pharmaceuticals Inc., Mylan Inc., and Mylan N.V. (collectively, “the Mylan Defendants”), Teva Pharmaceuticals USA, Inc. (“Teva”), Apotex Inc. and Apotex Corp. (collectively “Apotex”), Hetero Labs Limited, Hetero Labs Limited Unit-V, Hetero Drugs Limited, and Hetero USA, Inc. (collectively “Hetero”), Aurobindo Pharma Limited, Aurobindo Pharma USA, Inc., Aurolife Pharma LLC, and Eugia Pharma Specialties Limited (collectively “Aurobindo”), and Breckenridge Pharmaceutical, Inc. (“Breckenridge”) (collectively “Defendants”) provide to Plaintiff Celgene Corporation (“Celgene” or “Plaintiff”) the following invalidity contentions (the “Contentions”) with regard to the asserted claims of U.S. Patent Nos. 8,198,262 (“the ’262 patent”), 8,673,939 (“the ’939 patent”), 8,735,428 (“the ’428 patent”) and 8,828,427 (“the ’427 patent”) (collectively, “patents-in-suit”). Pursuant to Local Patent Rules 3.4(b)-(d) and 3.6(d), Defendants’ contentions are accompanied by a production of the prior art identified pursuant to Local Patent Rule 3.3(a) that does not appear in the file histories of the patents-in-suit and the other documents on which Defendants intend to rely in support of their invalidity contentions (DEFS_POM_00000001-DEFS_POM_00013787).

Defendants provide these contentions based on information reasonably available to them at the present time. Because fact discovery is ongoing, these Contentions may require subsequent amendment, alteration and supplementation. Plaintiff has asserted infringement of claims 1, 2, 4-16, 18-27, and 29 of the ’262 patent, claims 1-14 and 16-35 of the ’939 patent, claims 1-27 of the ’428 patent and claims 3-10 of the ’427 patent. As such, Defendants have only provided invalidity contentions regarding these asserted claims. However, if Plaintiff later asserts other claims, Defendants reserve the right to provide additional invalidity contentions regarding the same. Defendants reserve their right to supplement these Contentions and to

submit expert opinions and analyses on invalidity of the '262, '939, '428 and '427 patents in accordance with the schedule for expert discovery set by the Court. Furthermore, the excerpts of the prior art included or referenced in these Contentions are exemplary rather than exhaustive, and are listed without prejudice to Defendants' right to rely on any other portion of that prior art not cited herein. The Contentions are meant to be illustrative, and in no way limit Defendants' ability to rely on other portions of the '262, '939, '428 and '427 patents or other documents or information, such as other prior art evidencing the state of the art, in support of their invalidity claims.

Defendants reserve the right to supplement and/or amend these contentions, including the identification and production of additional documents, including prior art, at any time and for any reason. Among other things, Defendants reserve their right to amend, revise, correct, supplement, revise or amend these contentions based upon further investigation, any claim construction ruling by the Court,¹ any changes made to Pomalyst[®], and/or further information gathered during discovery, including discovery obtained from third parties. Defendants further reserve the right to supplement and/or amend these contentions in response to any contentions by Plaintiff. Defendants also reserve the right to supplement and/or amend these contentions as necessary and appropriate, including as discovery proceeds, if Celgene asserts additional infringement allegations or claims at a later date and as otherwise provided under the Local Patent Rules or any other applicable Rules or order of the Court. Defendants further reserve their rights to amend these contentions based on any discovery materials that have not yet been produced or provided to Defendants, including but not limited to Plaintiff's production of

¹ To the extent that the parties seek, or the Court adopts, claim constructions of terms that render unsupported the full scope of the claims in which those terms appear, then all such claims are invalid for lack of written description, enablement, or both under 35 U.S.C. § 112.

documents, including productions of Plaintiff's NDA, laboratory notebooks, reports, communications and samples of Pomalyst[®], which have not yet been produced or provided to Defendants. Defendants will take third party discovery and reserve the right to amend when that is completed. In addition, Defendants reserve the right to supplement and/or amend their contentions at any time and for any reason in accordance with the Local Patent Rules and during the expert discovery phase of the litigation. Defendants also reserve the right to supplement and/or amend these contentions as necessary and appropriate, including as discovery proceeds, if Celgene asserts claim contentions that are different from any assumptions that were compelled to be made herein as a result of the inverted procedures of Rule 3.6, and/or Celgene asserts constructions or additional or different infringement allegations at a later date, and as otherwise provided under the Local Patent Rules or any other applicable Rules or order of the Court. Defendants also reserve the right to supplement and/or amend these contentions as prior art is discovered and/or to develop the scope and content of the prior art.

By submitting these Contentions, Defendants do not waive any claims or defenses that may be asserted in this case. The information set forth below is provided without in any manner waiving the right to object to the use of any statement for any purpose, in this action or any other action. Defendants do not waive the right to object to any request involving or relating to the subject matter of these statements, or to revise, correct, supplement, or clarify any of the statements provided below at any time. These Contentions may be asserted in the alternative and do not constitute any concession by Defendants for purposes of claim construction, non-infringement, or invalidity, nor do Defendants waive any arguments that may be made or positions that may be taken regarding the proper construction of any claim term. These Contentions should not be interpreted as a statement of Defendants' position with regard to the

proper claim construction of any claim term. Instead, Defendants have made certain assumptions, to the extent necessary and appropriate, with respect to the meaning of claim terms for the purpose of these contentions only in the preparation of this statement. To the extent Defendants determine that a different meaning is appropriate for any claim term, Defendants will assert that meaning in connection with the claim construction proceedings, and further reserve the right to update these contentions as a result of the *Markman* proceedings, or any other disclosure or alteration of the meaning of claim terms.

Defendants incorporate, in full, all documents and prior art references cited in any one or more of the Patents-in-Suit, as well as any related patents and applications, including their respective prosecution histories, including those filed in the United States or in a foreign country and those listed for Pomalyst[®], Revlimid[®] or Thalomid[®] in the FDA's Orange Book. Defendants incorporate by reference all of the notice letters mailed to Celgene prior to the initiation of these actions. Specifically, Defendants incorporate by reference Teva's Notice Letter (and Detailed Statement) mailed to Celgene on March 30, 2017, Breckenridge's Notice Letter (and Detailed Statements Regarding the patents-in-suit) sent to Celgene on April 11, 2017, Mylan Pharmaceuticals Inc.'s Notice Letter (and Detailed Statement) mailed to Celgene on April 6, 2017, Aurobindo's Notice Letter (and Detailed Statement) mailed to Celgene on April 5, 2017, Apotex's Notice Letter (and Detailed Statement) dated Celgene dated March 30, 2017, and Hetero's Notice Letter (and Detailed Statement) sent to Celgene dated March 29, 2017.

These contentions are provided without prejudice to Defendants' right to introduce at trial any subsequently-discovered evidence or expert opinions relating to currently known facts or the state of the art, and to produce and introduce at trial all evidence, whenever discovered, relating to the proof of subsequently-discovered facts. Moreover, facts, documents and things now

known may be imperfectly understood and, accordingly, such facts, documents and things may not have been included in this statement. Defendants reserve their rights to refer to, conduct discovery with reference to, or offer into evidence at the time of trial, any and all facts, expert opinion testimony, documents and things notwithstanding this statement of Defendants' contentions. Defendants further reserve their rights to refer to, conduct discovery with reference to, or offer into evidence at the time of trial, any and all facts, documents and things that are not currently recalled but might be recalled at some time in the future. Defendants object to the disclosure of information that is protected by the attorney-client privilege, attorney work product immunity, or any other applicable privilege or immunity. To the extent Defendants inadvertently disclose information that may be protected from discovery under the attorney-client privilege, attorney work product immunity, or any other applicable privilege or immunity, such inadvertent disclosure does not constitute a waiver of any such privilege or immunity.

Defendants disclose detailed Contentions with respect to each asserted claim of the '262, '939, '428 and '427 patents in Exhibits A-D, attached. The citations to particular portions of the prior art included in those charts are intended to be exemplary rather than exhaustive, and Defendants reserve the right to rely on any other portions of those prior art references whether or not cited in the charts. In the Contentions and claim charts that follow, the Contentions and charts for any dependent claim also incorporate the Contentions and charts for any claim from which the dependent claim depends. This includes all prior art and non-prior art defenses.

Defendants are not aware of any applicable objective indicia of non-obviousness at this stage. Defendants maintain that for purposes of these Contentions, Defendants have no burden to come forward with evidence rebutting the obviousness of the Patents-in-Suit or any evidence of secondary considerations of non-obviousness that Plaintiff may assert, since Plaintiff has the

burden of initially coming forward with evidence of any secondary considerations of non-obviousness that it intends to rely on. Defendants reserve all rights to respond to any objective indicia of non-obviousness that Plaintiff may later assert. Should Plaintiff identify any objective indicia of non-obviousness, Defendants reserve all rights to respond to and rely upon further references not cited herein to rebut those objective indicia of non-obviousness.

I. IDENTIFICATION OF PRIOR ART PURSUANT TO L. PAT. R. 3.3(a)

Pursuant to Local Patent Rule 3.3(a), Defendants identify prior art presently known to Defendants that anticipates one or more of the asserted claims or renders one or more of the asserted claims obvious. Defendants reserve the right to rely on these and additional references as they become known, or become necessary, in responding to Celgene's contentions, proposed claim construction, and/or witness testimony, including responding to Celgene's expert witness testimony.

Defendants also reserve the right to rely on any of the references identified below or cited in the specification or on the face of any of the Patents-in-Suit, or combinations thereof. By way of example only and not by way of limitation, Defendants' experts might rely on references identified below for, *inter alia*, any and all of the following purposes: scope and content of the prior art; level of ordinary skill in the art; the knowledge of the person of ordinary skill in the art; inherency; suggestion, teaching, or motivation to combine; reasonable expectation of success; common knowledge, the prior art as a whole, or the nature of problems; and/or responding to Celgene's assertion, if any, of differences between the claimed invention and prior art and/or objective indicia of non-obviousness. Defendants' experts may also rely on additional references, not identified below, when describing the scope and content of the prior art or the knowledge of the person having ordinary skill in the art; when providing a tutorial to the Court at trial or any other hearing; or in responding to any responsive contentions by Celgene, such as

contentions regarding non-enablement of prior art, objective indicia of non-obviousness, or for any other purpose.

Defendants also reserve the right to rely on any of the admitted prior art in the Patents-in-Suit. For example, the Zeldis Patents admit that it was known that many types of cancer are associated with angiogenesis, that several mechanisms involved in angiogenesis were also known, and that controlling angiogenesis or inhibiting certain mechanisms would be useful in the treatment of such conditions. *See, e.g.*, '262 patent, 1:53-2:17. It was also known that one problem with cancer treating agents is their toxicity and that "almost all chemotherapeutic agents are toxic." *See, e.g., id.* at 2:48-54. Likewise, drug resistance was also a known and well-studied condition. *See, e.g., id.* at 2:54-64. Thalidomide and certain derivatives were also known for the treatment of cancer and undesired angiogenesis. *See, e.g., id.* at 2:65-3:37. In particular, IMiDs were known to be safe and effective in treating cancer and undesired angiogenesis, and were known to have various beneficial mechanisms of action useful in such treatment. *See, e.g., id.* The Zeldis Patents also admit that both lenalidomide and pomalidomide were known, publicly available, and made by known methods. *See, e.g.*, '262 patent, 9:50-55 ("Compounds of the invention can ... be commercially purchased or prepared according to the methods described in the patents or patent publications disclosed herein."). Likewise, dexamethasone or Decadron® was a known, commercially available second active agent. *See, e.g., id.* at 15:61. Additionally, various types of dosage forms, as well as various excipients and their suitable amounts, were well-known. *See, e.g.*, '262 patent at 25:45-30:36, '427 Patent at 4:49-12:14.

A. Prior Art Patents, Publications, Inventions and Products

The following references are prior art to the Patents-in-Suit under one or more of 35 U.S.C. §§ 102(a), (b), (e), (f) and (g). Additionally, the compounds disclosed in the following

references are also prior art, whether or not the compounds or their chemical structure are specifically identified in the below references. For example, various journals and conferences require that as a condition of publication the author make the described compounds publicly available. *See, e.g.*, Blood Editorial Policies (2001) (“any readily renewable resources mentioned in a Journal article that is not already obtainable from commercial sources shall be made available to all qualified investigators in the field”). Thus, the composition would have been available to the POSA at least as of the time of publication. These prior art references anticipate or, alone or in combination, render obvious one or more of the Asserted Claims. Defendants reserve the right to rely on additional references and documents not listed or described herein as evidence of the scope and content of the prior art, the knowledge of the person having ordinary skill in the art, to demonstrate the motivation to combine prior art references, and to rebut any evidence of validity raised by Celgene.

1. Muller, G., et al., *Amino-Substituted Thalidomide Analogs: Potent Inhibitors of TNF- α Production*, Biorg. Med. Chem. Lett., 9:1625-1630 (1999) (“Muller”); [DEFS_POM_00011054-059]
2. U.S. Patent No. 5,635,517 (“the ’517 patent”); [DEFS_POM_00000175-185]
3. U.S. Patent No. 5,731,325 (“the ’325 patent (Andrulis)”); [DEFS_POM_00000149-156]
4. U.S. Patent No. 6,316,471 (“the ’471 patent”); [DEFS_POM_00000157-174]
5. Rajkumar, et al., Abstract #722, Thalidomide plus dexamethasone (Thal/Dex) and thalidomide alone (thal) as first line therapy for newly diagnosed myeloma (MM), Blood, 96(11):168a (2000) (“Rajkumar”); [DEFS_POM_00011159-160]
6. Durie, B.G.M., and Stepan, D.E., *Efficacy of low dose thalidomide in multiple myeloma*, Electronic Journal of Oncology, 1:1-8 (2000) (“Durie”); [DEFS_POM_00003826-833]
7. Palumbo, A., et al., Low-dose thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma, Haematologica, 86:399-403 (2001) (“Palumbo”); [DEFS_POM_00011142-146]

8. Singhal, S., et al., *Antitumor activity of thalidomide in refractory multiple myeloma*, N. Engl. J. Med., 341:1565-1571 (1999) (“Singhal”); [DEFS_POM_00011432-438]
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10. Corral, L.G., et al., *Differential Cytokine Modulation and T Cell Activation by Two Distinct Classes of Thalidomide Analogs That Are Potent Inhibitors of TNF- α* , J. of Immunology, 163:380-386 (1999) (“Corral I”); [DEFS_POM_00013259-266]
11. Corral, L.G., et al., *Immunomodulation by thalidomide and thalidomide analogues*, Ann. Rheum. Dis., 58 (Suppl. I): I107- I113 (1999) (“Corral II”); [DEFS_POM_00002190-196]
12. Weber, et al., Abstract #719, *Thalidomide with dexamethasone for resistant multiple myeloma*, Blood, 96(11):167a (2000) (“Weber 2000”); [DEFS_POM_00012320-322]
13. Rajkumar, S.V., and Kyle, R.A., *Thalidomide in the treatment of plasma cell malignancies*, J. of Clinical Oncology, 19(16):3593- 3595 (2001) (“Rajkumar & Kyle”); [DEFS_POM_00013404-406]
14. Kropff, et al., Abstract #725, *Hyperfractionated cyclophosphamide in combination with pulsed dexamethasone and thalidomide (hyper- CDT) in primary refractory or relapsed multiple myeloma*, Blood, 96(11):168a (2000) (“Kropff”); [DEFS_POM_00011003-004]
15. Klausner, et al., *The Effect of Thalidomide on the Pathogenesis of Human Immunodeficiency Virus Type I and M. tuberculosis Infection*, J. of Acquired Immune Deficiency Syndromes and Human Retrovirology, 11:247-257 (1996) (“Klausner I”); [DEFS_POM_00010983-997]
16. Klausner, et al., *Short analytical review: thalidomide as an anti-TNF- α inhibitor: implications for clinical use*, Clinical Immunology and Immunopathology, 81(3):219-223 (1996) (“Klausner II”); [DEFS_POM_00010998-1002]
17. Market Letter (June 18, 2001), *Celgene drug promises activity in solid tumors*, (Market Publications Ltd.) (“June Market Letter”); [DEFS_POM_00013346-348]
18. Market Letter (October 15, 2001), *Celgene’s Revlimid an orphan drug, says FDA*, (Market Publications Ltd.) (“October Market Letter”); [DEFS_POM_00013394-396]
19. Hideshima, T., et al., *The Proteasome Inhibitor PS-341 Inhibits Growth, Induces Apoptosis, and Overcomes Drug Resistance in Human Multiple Myeloma Cell*,

- Cancer Research, 61:3071–3076 (2001) (“Hideshima 2001”); [DEFS_POM_00013313-318]
20. PCT Publication WO 98/03502 (“WO 98/03502”); [DEFS_POM_00012323-370]
21. Marriott, et al., *Immunotherapeutic and antitumour potential of thalidomide analogues*, Expert Opinion on Biological Therapy, 1(4):675-682 (2001) (“Marriott 2001”); [DEFS_POM_00013372-380]
22. D’Amato, et al., *Mechanism of Action of Thalidomide and 3-Aminothalidomide in Multiple Myeloma*, Seminars in Oncology, 28(6):597-601 (2001) (“D’Amato 2001”); [DEFS_POM_00002201-205]
23. Aviles, et al., *Dexamethasone, all trans retinoic acid and interferon alpha 2a in patients with refractory multiple myeloma*, Cancer Biotherapy & Radiopharmaceuticals, 14(1):23-26 (1999) (“Aviles”); [DEFS_POM_00001749-753]
24. Thalomid Product; [DEFS_POM_00000018-22; DEFS_POM_00000023-44; DEFS_POM_00000051-74; DEFS_POM_00000075-94; DEFS_POM_00000126-129; DEFS_POM_00012565-93]
25. Dimopoulos, et al., *Thalidomide and dexamethasone combination for refractory multiple myeloma*, Ann Oncology, 12:991- 995 (2001) (“Dimopoulos”); [DEFS_POM_00002206-210]
26. 42nd annual meeting of the American Society of Hematology, Abstract # 3617, Abstracts # 2485-87 (2000) (“2000 Abstracts”); [DEFS_POM_00000045-050]
27. Davies, et al., *Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma*, Blood, 98:210-216 (July 2001) (“Davies”); [DEFS_POM_00013267-274]
28. Fujita, et al., *Thalidomide and its analogues inhibit lipopolysaccharide-mediated induction of cyclooxygenase-2*, Clinical Cancer Research, 7:3349–3355 (2001) (“Fujita”); [DEFS_POM_00013285-291]
29. Stirling, et al., *Thalidomide: A Novel Template for Anticancer Drugs*, Seminars in Oncology, 28:602-606 (2001) (“Stirling”); [DEFS_POM_00011465-469]
30. Richardson, et al., Abstract #3225-3226, A phase 1 study of oral CC5013, an immunomodulatory thalidomide (Thal) derivative, in patients with relapsed and refractory multiple myeloma (MM), Blood, 98:775a (2001) (“Richardson I”); [DEFS_POM_00011170-172]
31. Gupta, et al., *Adherence of multiple myeloma cells to bone marrow stromal cells upregulates vascular endothelial growth factor secretion: therapeutic applications*, Leukemia, 15:1950–1961 (2001) (“Gupta”); [DEFS_POM_00010950-961]

32. Dredge, et al., Protective anti-tumor immunity induced by a costimulatory thalidomide analog in conjunction with whole tumour cell vaccination is mediated by increased Th1-type immunity, *J. of Immunology*, 168:4914-4919 (2002) (“Dredge 2001”); [DEFS_POM_00013275-281]
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34. Dredge, et al., *Thalidomide analogs as emerging anti-cancer drugs*, *Anticancer Drugs*, 14:331-335 (2003) (“Dredge 2003”); [DEFS_POM_00003807-811]
35. Mitsiades, et al., Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications, *Blood*, 99:4525-4530 (2002) (“Mitsiades”); [DEFS_POM_00013381-387]
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37. Raje, N. and Anderson, K.C., *Thalidomide and immunomodulatory drugs as cancer therapy*, *Current Opinion in Oncology*, 14:635-640 (2002) (“Raje”); [DEFS_POM_00011147-152]
38. Richardson, et al., Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma, *Blood*, 100:3063-3067 (2002) (“Richardson II”); [DEFS_POM_00011173-177]
39. Richardson, et al., *Thalidomide in Multiple Myeloma*, *Biomed Pharmacotherapy*, 56:115-28 (2002) (“Richardson III”); [DEFS_POM_00011178-191]
40. Marriott, et al., Thalidomide and its analogues have distinct and opposing effects on TNF-alpha and TNFR2 during co-stimulation of both CD4⁺ and CD8⁺ T cells, *Clin. Exp. Immunology*, 130:75-84 (2002) (“Marriott 2002”); [DEFS_POM_00011039-048]
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42. Schey, S.A., *Thalidomide in the management of multiple myeloma*, *Hematology* 7(5):291-299 (October 2002) (“Schey II”); [DEFS_POM_00013475-484]
43. Schey, S.A., et al., *Phase I Study of an Immunomodulatory Thalidomide Analog, CC-4047, in Relapsed or Refractory Multiple Myeloma*, *J. of Clinical Oncology*, 22(16):3269-3276 (2004) (“Schey III”); [DEFS_POM_00013485-492]

44. Celgene Annual Report 1999 (“Celgene Annual Report 1999”); [DEFS_POM_00001777-798]
45. Celgene Press Releases, various dates since September 3, 1998 (“Celgene Press Releases”); [DEFS_POM_00001799-870; DEFS_POM_00013252-258]
46. Lentzsch, et al., Abstract # 1976, *S-3-Amino-phthalimido-glutarimide Inhibits Growth in Drug Resistant Multiple Myeloma (MM) In Vivo*, Blood, 43rd Annual Amer. Soc. Hematol. (Dec. 7-11, 2001), 98(11): 473a (2001) (“Lentzsch 2001”); [DEFS_POM_00011018-019]
47. Lentzsch, S., et al., *S-3-Amino-phthalimido-glutarimide Inhibits Angiogenesis and Growth of B-Cell Neoplasias in Mice*, Cancer Research, 62:2300-2305 (2002) (“Lentzsch 2002”); [DEFS_POM_00013366-371]
48. Sorbera, et al., *CC-5013*, Drugs of the Future, 28(5):425-431 (2003) (“Sorbera”); [DEFS_POM_00011458-464]
49. Anderson K., *The role of Immunomodulatory Drugs in Multiple Myeloma*, Semin. Hematol., 40(4):23-32 (2003) (“Anderson”); [DEFS_POM_00000339-348]
50. Richardson, P., et al., Abstract #386, A Multi-Center, Randomized, Phase II Study To Evaluate the Efficacy and Safety of Two CDC-5013 Dose Regimens When Used Alone or in Combination with Dexamethasone (Dex) for the Treatment of Relapsed or Refractory Multiple Myeloma (MM), Blood, 100 (11, Part 1): 104a (2002); (“Richardson IV”); [DEFS_POM_00011192-194]
51. U.S. Patent No. 5,712,291 (“the ’291 patent”); [DEFS_POM_00000130-148]
52. Robert, F., et al., Phase I and pharmacologic study of 7- and 21-day continuous etoposide infusion in patients with advanced cancer, Cancer Chemotherapy Pharmacology, 38(5):459-65 (1996) (“Robert”); [DEFS_POM_00011224-230]
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54. Lee, et al., A pilot trial of hyperfractionated thoracic radiation therapy with concurrent cisplatin and oral etoposide for locally advanced inoperable non-small-cell lung cancer: a 5-year follow-up report, Int. J. Radiat. Oncol. Biol. Phys., 42(3):479-86 (1998) (“Lee”); [DEFS_POM_00011010-017]
55. The Chemotherapy Source Book (Michael C. Perry Ed., 1992) (“Chemotherapy 1992”); [DEFS_POM_00002148-151]

56. Weber, et al., Abstract #2686, *Thalidomide Alone or With Dexamethasone for Multiple Myeloma*, Blood, 94(1):604a (1999) (“Weber 1999”); [DEFS_POM_00013539-541]
57. U.S. Patent No. 4,551,177 (“the ’177 patent”); [DEFS_POM_00000001-017]
58. Hus, et al., *Thalidomide treatment of resistant or relapsed multiple myeloma patients*, Haematologica, 86:404-408 (2001) (“Hus”); [DEFS_POM_00013319-323]
59. Oken, et al., Comparison of melphalan and prednisone with vincristine, carmustine, melphalan, cyclophosphamide, and prednisone in the treatment of multiple myeloma, Cancer, 79:1561-1567 (1997) (“Oken”); [DEFS_POM_00013397-403]
60. Alkeran 2001 Label (“Alkeran 2001 Label”); [DEFS_POM_00000331-338]
61. Knight, J., *Cancer Patients Ahead of FDA on Thalidomide Use*, Washington Post, June 25 2001 (“Knight”); [DEFS_POM_00013354-358]
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64. PCT Publication WO 02/059106 (“WO 02/059106”); [DEFS_POM_00013564-787]
65. PCT Publication WO 02/064083 (“WO 02/064083”); [DEFS_POM_00012371-412]
66. PCT Publication WO 02/43720 (“WO 02/43720” or “Hwu”); [DEFS_POM_00012413-467]
67. Hideshima et al., Abstract # 1313, Thalidomide (Thal) and its Analogs overcome Drug Resistance of Human Multiple Myeloma (MM) Cells to Conventional Therapy, Blood, 96(11): 304a (2000) (“Hideshima Abstract”); [DEFS_POM_00010981-982]
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B. Scope and Content of the Prior Art

Certain prior art references are described in further detail below. Defendants reserve the right to rely on any of the above listed references as anticipating or rendering obvious one or more of the Asserted Claims.

1. Muller

Muller discloses that a structural analog of thalidomide, identified as “compound 5a,” demonstrated more potent inhibition of TNF- α than thalidomide. Muller at 1627. TNF- α is a key cytokine in the inflammatory cascade and elevated TNF- α levels are associated with inflammatory diseases. Muller discloses that thalidomide has an IC₅₀ of about 200 μ M in inhibiting TNF- α production from LPS stimulated Peripheral Blood Mononuclear Cells (PBMCs). Muller at 1628. Compound 5a was reported to have an IC₅₀ of 13 nM in the LP stimulated PBMC assay, meaning that pomalidomide is a more potent inhibitor of TNF- α . *Id.* at 1629. In particular, Muller states that the “(S)-4-amino substituted analog of 5a was found to be ~50,000 times more potent than thalidomide at inhibiting TNF- α levels in LPS stimulated human PBMC.” *Id.* Muller discloses that “thalidomide has been found to afford clinical benefit in a variety of autoimmune and inflammatory disease states.” *Id.* at 1625.

Muller qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(b), having published in 1999, which is more than a year before the earliest possible priority date.

2. The '517 patent

U.S. Patent No. 5,635,517 (“the '517 patent”) is titled “Method of Reducing TNF α Levels With Amino Substituted 2-(2,6-dioxopiperidin-3-yl)-1-Oxo-and 1,3-dioxoisindolines,” and is listed in the Orange Book by Celgene for Pomalyst and Revlimid. The '517 patent discloses a method of reducing undesirable levels of TNF- α in a mammal comprising administering pomalidomide (1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisindoline). '517 patent 12:8-10. The '517 patent discloses pomalidomide in Formula I when both X and Y are C=O, as well as other derivatives of thalidomide. *Id.* at 4:25-32. The '517 patent discloses that pomalidomide can be administered orally to reduce TNF- α , *id.* at 4:37-40, 6:35-37, and can be administered in the form of a capsule or tablet, *id.* at 6:35-37. The '517 teaches that the described compounds, including pomalidomide, can be used to treat cancer. *Id.* 3:58-4:11. The '517 patent also teaches that pomalidomide can be administered in oral dosage forms that include tablets or capsules containing from 1 to 100 mg of drug per unit dosage. *Id.* at 6:35-37. The '517 patent further teaches that pomalidomide can be administered in combination with other active compounds such as antibiotics and steroids. *Id.* at 4:37-40. Dexamethasone is a steroid. Additionally, the '517 patent discloses the structure of pomalidomide in Formula I of the specification and in claim 1 in non-protonated, free base form. *Id.* at 4:25-30, 11:2-7. The '517 patent also directly claims treatment with pomalidomide in claim 8.

The '517 patent qualifies as prior art to the '262, '939, '428, and '427 patents under at least 35 U.S.C. § 102(b), having issued on June 3, 1997, which is more than a year before the earliest possible priority date.

3. The '325 patent (Andrulis)

The '325 patent (Andrulis) is titled “Treatment of Melanomas With Thalidomide Alone or in Combination With Other Anti-Melanoma Agents.” The '325 patent (Andrulis) discloses

the use of thalidomide for the treatment of melanomas with doses that “are typically 50 mg to 1000 mg and preferably 100 mg to 750 mg two to three times a day.” *See, e.g.*, ’325 patent (Andrulis) at Abstract, 6:60-63. The use of cycles of thalidomide to treat melanoma was also disclosed in the ’325 patent (Andrulis), “[t]he term ‘therapeutic cycle’ when used in the present specification, refers to a 28-day or other cycle wherein thalidomide or a combination of thalidomide with other anti-melanoma agents is administered to a patient.” *Id.* at 6:3-11. The ’325 patent (Andrulis) further discloses a clinical trial protocol involving the treatment of melanoma with cycles of thalidomide that lasted for 7, 21, or 28 days depending on the degree of malignancy. *Id.* at 13:1-19. Additionally, the ’325 patent (Andrulis) discloses the combination of thalidomide with other cytokine/growth factor inhibitor therapies, including dexamethasone and pentoxifylline. *Id.* at 7:12-23.

The ’325 patent (Andrulis) patent qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(b), having issued on March 24, 1998, which is more than a year before the earliest possible priority date.

4. The ’471 patent

U.S. Patent No. 6,316,471 (“the ’471 patent”) is titled “Isoindolines, Method of Use, and Pharmaceutical Compositions,” is listed in the Orange Book by Celgene for Pomalyst and expired in 2016. The ’471 patent teaches the use of certain compounds including pomalidomide in the treatment of autoimmune diseases and cancers. The ’471 patent discloses pomalidomide in claim 1 and in the specification as Formula I when both X and Y are C=O in non-protonated free base form, as well as other derivatives of thalidomide. ’471 patent at 4:45-55 and 27:55-60. The ’471 patent also discloses that pomalidomide can be administered orally to reduce TNF- α , *id.* at 5:25-30, and can be administered in the form of a capsule or tablet containing from 1 to 100 mg of drug per unit dosage, *id.* at 8:26-28 and 28:65-67. The ’471 patent discloses that

decreasing TNF- α constitutes a valuable therapeutic strategy to treat cancer. *Id.* at 28:25-37. Claim 1 is directed to methods of treatment using pomalidomide, and claim 16 is directed to the use of pomalidomide to treat an oncogenic or cancerous condition. The '471 patent also teaches that pomalidomide and lenalidomide can be administered in combination with other active compounds such as antibiotics and steroids, such as dexamethasone. *Id.* at col. 4:34, 5:27-30, 28:19-20, 28:44-45, and 29:3-4.

At the time the USPTO issued the '471 patent, Celgene announced that the claims of that patent cover “the use of ACTIMID™ (CDC 394), Celgene’s next IMiD™, to treat cancer and inflammatory diseases both as a single agent and in combination with other therapies.” *See* Celgene Press Release (Nov. 13, 2001) [DEFS_POM_00001808-809]. ACTIMID is pomalidomide. Celgene reported that ACTIMID™ (i.e., pomalidomide) was being evaluated at Guy’s Hospital in London in Phase I/II trials for the treatment of refractory multiple myeloma. *Id.*

The '471 patent qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a) or § 102(b), having issued on November 13, 2001.

5. Rajkumar

Rajkumar discloses that thalidomide combined with 40 mg dexamethasone administered on days 1-4, 9-12, 17-20 (odd cycles) and days 1-4 (even cycles), repeated monthly, was effective against new, untreated multiple myeloma (or “MM”). Rajkumar at 168a. Thalidomide was administered orally. *Id.* The authors report that the results also appear to show greater efficacy for the combination of thalidomide and dexamethasone than for thalidomide alone. *Id.*

Rajkumar qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 2000, which is more than a year before the earliest possible priority date.

6. Durie

Durie discloses a study to evaluate thalidomide at doses between 50 mg and 400 mg/day with dose escalation based only upon lack of response in myeloma patients. The study showed that “[l]ow dose thalidomide is generally well tolerated and can induce excellent remission in 25% of relapsing or refractory myeloma patients.” Durie at 1. Durie stated that “[t]he benefit of thalidomide was particularly evident in patients who had previously received stem cell transplantation.” *Id.* at 4. Some patients achieved excellent remission with thalidomide administration of 50 mg/day. *Id.* at 6. Durie also discloses that, when treating multiple myeloma, the addition of 40 mg dexamethasone (daily for 4 days, twice a month) provided synergistic results. *Id.* at 4, 7.

Durie qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(b), having published in 2000, which is more than a year before the earliest possible priority date.

7. Palumbo

Palumbo discloses effective treatment of refractory and relapsed multiple myeloma patients using low-dose thalidomide daily for a month-long cycle in combination with 40 mg of dexamethasone per day on days 1-4 of the cycle. Palumbo at 399. That is, “[t]halidomide was administered at the dose of 100 mg at bedtime and associated with dexamethasone administered orally at the dose of 40 mg on days 1, 2, 3, and 4 every month.” *Id.* at 400. Palumbo evaluated the toxicity and clinical efficacy of low-dose thalidomide (100 mg/day) combined with corticosteroids (dexamethasone) on the assumption that lower thalidomide doses are better tolerated and the association with corticosteroids may exert a synergistic effect. *Id.* at 399. Refractory/relapsed myeloma patients were treated with this 100 mg/day schedule. *Id.* at 400. Low-dose thalidomide plus dexamethasone was shown to be extremely well tolerated and highly

effective. *Id.* at 401. A dose of 50 mg/day was shown to be effective in myeloma patients. *Id.* at 402. Palumbo discloses that amongst the patients, “41% showed a myeloma protein decline >50%; in 18% the decline was 75-100%, in 23% it was 50-75%, and in 25% it was 25-50%.” *Id.* at 400. Palumbo thus concludes that “we demonstrate that the combination of thalidomide at 100 mg/day plus dexamethasone at only 40 mg, 4 days each month, is an effective treatment against myeloma.” *Id.* at 402.

Palumbo further discloses that “[t]wenty-six patients received thalidomide after one line of therapy, 21 after two and 30 after three. Among those receiving high-dose chemotherapy, 17 were in first untested relapse, 18 in second untested relapse and 2 were in resistant relapse. Of those treated with conventional chemotherapy, 4 had primary resistance, 19 were in resistant relapse and 17 in untested relapse.” *Id.* at 400. Additionally, Palumbo discloses that “[t]halidomide and dexamethasone are a logical combination since they may differ in their action against myeloma. Thalidomide acts via adhesion molecule alteration, anti-angiogenesis and modulation of T-lymphocytes, whereas dexamethasone exerts its effect by inhibiting IL-6 production.” *Id.* at 402. Additionally, Palumbo notes that “[i]n vitro, the addition of dexamethasone increased the inhibition of proliferation induced by thalidomide on myeloma cell lines by about 35%. Thalidomide induced apoptosis in cells resistant to dexamethasone, suggesting the potential utility of the combination of these two drugs.” *Id.*

Palumbo qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in April 2001, which is more than a year before the earliest possible priority date.

8. Singhal

Singhal discloses the antitumor activity of thalidomide in patients with refractory multiple myeloma, most of whom had received at least one cycle of high-dose chemotherapy

with autologous hematopoietic stem cell support. Singhal at 1565. Singhal states that “[p]atients with myeloma who relapse after high-dose chemotherapy have few therapeutic options. Since increased bone marrow vascularity imparts a poor prognosis in myeloma, we evaluated the efficacy of thalidomide, which has antiangiogenic properties, in patients with refractory disease.” Singhal at Abstract. Singhal states that in its methods, patients were dosed with thalidomide in ranges of 200-800 mg/day. *Id.* at 1566. Singhal states that “[w]e found that thalidomide had substantial antitumor activity in patients with advanced myeloma.” *Id.* at 1569. Singhal further explains “[t]halidomide has a number of properties that could explain its activity in myeloma; it can alter the expression of adhesion molecules, suppress the production of tumor necrosis factor α , increase the production of interleukin-10, and enhance cell-mediated immunity by directly stimulating cytotoxic T cells.” *Id.* at 1570.

Singhal concludes that “thalidomide is active against multiple myeloma, even in patients who relapsed after repeated cycles of high-dose chemotherapy. Larger studies of thalidomide, its analogues, and other inhibitors of anti-angiogenesis are therefore warranted in patients with myeloma and other cancers. We are currently evaluating thalidomide in combination with chemotherapy for patients with newly diagnosed multiple myeloma.” Singhal at 1571.

Singhal qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(b), having published in 1999, which is more than a year before the earliest possible priority date.

9. **Hideshima 2000**

Hideshima 2000 demonstrates clinical activity of thalidomide and three analogs, IMiD1, IMiD2, and IMiD3 (pseudonyms for pomalidomide and lenalidomide), against multiple myeloma that is refractory to conventional therapy. Hideshima 2000 at 2943, 2946. Hideshima also evaluates the effects of thalidomide and these analogs on multiple myeloma cells in

combination with dexamethasone and IL-6. *Id.* Hideshima 2000 teaches that “studies demonstrate clinical activity of Thal against MM that is refractory to conventional therapy and delineate mechanisms of anti-tumor activity of Thal and its potent analogs (immunomodulatory drugs [IMiDs]). ... Thal and the IMiDs enhance the anti-MM activity of Dex [dexamethasone].” Hideshima at Abstract. Hideshima 2000 observes that IMiDs significantly inhibited uptake in multiple myeloma cells, and that dexamethasone further increased the inhibition of proliferation, giving it an “additive effect.” *Id.* at 2946. Hideshima 2000 discloses *in vitro* tests showing that both thalidomide and its IMiDs show anti-multiple myeloma activity and enhance the anti-multiple myeloma activity of dexamethasone. *Id.* at 2949. The authors found that all three IMiDs (IMiD1, IMiD2, and IMiD3) tested achieved 50% inhibition of DNA synthesis in multiple myeloma cells *in vitro*, confirming their direct action on tumor cells and suggesting their clinical utility. *Id.* at 2949. Moreover, the IMiDs inhibited the proliferation of dexamethasone-resistant multiple myeloma cells by 50%. *Id.* The authors also concluded that the IMiDs “enhance the anti-MM activity of Dex.” *Id.* at 2943. Hideshima 2000 cites to Corral I as testing the same IMiDs. *Id.* at 2944. Hideshima teaches that “IMiD1, IMiD2, and IMiD3 inhibited H-TdR uptake of MM.1S (Figure 1A) and Hs Sultan (Figure 1B) cells in a dose-dependent fashion. Fifty percent inhibition of proliferation of MM.1S cells was noted at 0.01-0.1 $\mu\text{mol/L}$ IMiD1, 0.1-1.0 $\mu\text{mol/L}$ IMiD2, and 0.1-1.0 $\mu\text{mol/L}$ IMiD3 ($P < .001$). Fifty percent inhibition of proliferation of Hs Sultan cells was noted at 0.1 $\mu\text{mol/L}$ IMiD1, 1.0 $\mu\text{mol/L}$ IMiD2, and 1.0 $\mu\text{mol/L}$ IMiD3 ($P < .001$). In contrast, only 15% and 20% inhibition in MM.1S and Sultan cells, respectively, were observed in cultures at even higher concentrations (100 mmol/L) of Thal.” *Id.* at 2945.

Hideshima 2000 further discloses that “[r]ecent reports of increased bone marrow (BM) angiogenesis in multiple myeloma (MM), coupled with the known antiangiogenic properties of Thal [thalidomide], provided the rationale for its use to treat MM.” Hideshima 2000 at 2943 (citation omitted). Hideshima 2000 reports that “Thal induced clinical responses in 32% of MM patients whose disease was refractory to conventional and high-dose therapy, suggesting that it can overcome drug resistance because of its alternative mechanisms of anti-MM activity.” *Id.* (citation omitted). Hideshima 2000 also discloses that “2 classes of Thal analogs have been reported, including phosphodiesterase 4 inhibitors that inhibit TNF- α but do not enhance T-cell activation (selected cytokine inhibitory drugs [SelCIDs]) and others that are not phosphodiesterase 4 inhibitors but markedly stimulate T-cell proliferation as well as IL-2 and IFN- γ production (immunomodulatory drugs [IMiDs]).” *Id.* (citation omitted). Hideshima 2000 states that “we have begun to characterize the mechanisms of activity of Thal and these analogs against human MM cells.” *Id.*

Hideshima 2000 conducted a number of experiments to elucidate the mechanism of thalidomide, SelCIDs and IMiDs against multiple myeloma cells, and report:

Our studies demonstrate that Thal and the IMiDs are acting directly on MM cells, in the absence of accessory BM or T cells. It is also possible that these agents may be mediating their anti-MM effect by cytokines, given their known inhibitory effects on TNF- α , IL-13, and IL-6. Our prior studies have characterized the growth effects of IL-6 on human MM cells, and we, therefore, next determined the effect of exogenous IL-6 on drug activity. Our studies showed that IL-6 can overcome the effect of Thal and the IMiDs on MM cell lines and patient cells, suggesting that these novel drugs may, at least in part, be inhibiting IL-6 production. Our prior studies have further demonstrated that IL-6-induced proliferation of MM cells is mediated through the MAPK cascade and that blockade of this pathway with either MAPK antisense oligonucleotide or the MEK1 inhibitor PD98059 can abrogate this response. The present study showed constitutive MAPK phosphorylation in MM cells that is inhibited by PD98059 and, to a lesser extent, by the IMiDs. Importantly, IL-6-triggered MAPK tyrosine phosphorylation is also blocked by PD98059 but not by IMiDs. These studies, therefore, suggest that the IMiDs do not work only by directly

inhibiting MAPK growth signaling and further support their potential activity in down-regulating IL-6 production. In MM, IL-6 production in tumor cells can either be constitutive or induced, mediating autocrine tumor cell growth. In addition, IL-6 is also produced by BM stromal cells in MM, a process that is up-regulated by tumor cell adhesion to BM stromal cells, with related tumor cell growth in a paracrine mechanism. Our ongoing studies are, therefore, evaluating the effect of Thal and these analogs on IL-6 production in the BM microenvironment.

Having shown the inhibitory effects of Thal and the IMiDs on H-TdR uptake of tumor cells, we next examined their effect on MM cell cycle. Interestingly, these drugs had distinct functional sequelae in MM cells. Specifically, the IMiDs, and to a lesser extent Thal, induced apoptosis of MM.1S cells, evidenced both by increased sub-G1 cells on PI staining and increased annexin V-positive cells. In these cells that have wt p53, these agents (and Dex) down-regulate p21, thereby facilitating G1-to-S transition and susceptibility to apoptosis. This apoptotic effect may correlate with the clinical observation that complete response to Thal is rarely observed. IL-6 overcomes the down-regulation of p21 induced by these agents, consistent with the increase in DNA synthesis triggered by IL-6 even in the presence of these drugs. In contrast, in Hs Sultan cells (wt and mt p53) and patient cells (wt p53 and mt p53), the IMiDs and Thal induce p21 and related G1 growth arrest, thereby conferring protection from apoptosis, as has been observed in other systems. In our prior study, p21 was also constitutively expressed in the majority of MM cells and also inhibited proliferation in both p53-dependent and independent mechanisms. Previous reports that cells overexpressing p21 protein demonstrate chemoresistance further support the protective effect of G1 growth arrest induced by these agents in Hs Sultan MM cells and patient MM cells. Conversely, the frequent regrowth of progressive MM noted clinically on discontinuation of Thal treatment may correlate with release of drug-related G1 growth arrest. An ongoing clinical trial is correlating response to Thal with laboratory parameters (ie, serum IL-6 or the surrogate marker C reactive protein) and will gain further insights into its mechanisms of in vivo anti-tumor activity.

Finally, our prior studies have characterized apoptotic signaling cascades in MM, as well as the protective effect of IL-6, especially against Dex-induced apoptosis. Specifically, we have shown that Dex down-regulates growth kinases, such as MAPK and p70RSK; importantly, it activates RAFTK, which is required for Dex-induced apoptosis and abrogated by IL-6. The current studies show that IMiD1 acts similarly to Dex, because it activates RAFTK and apoptosis in MM.1S cells, sequelae that are blocked by IL-6. Given our prior studies, which demonstrate that apoptosis of MM cells induced by UV irradiation, γ irradiation, and Fas ligation do not involve RAFTK, the current signaling studies, therefore, further support both the ability of the IMiDs to act through distinct signaling cascades to overcome drug resistance, as well as the

enhanced anti-tumor activity observed when Thal or the IMiDs are coupled with Dex.

In conclusion, the results of this study, therefore, demonstrate evidence for direct activity of Thal and the IMiDs against human MM cells. To confirm their in vivo mechanism of action, these compounds and SelCIDs will be examined in an animal model. Importantly, these studies provide the framework for the development and testing of a new biologically based treatment paradigm that uses these novel agents, either alone or together with conventional therapies, to target both the tumor cell and its microenvironment, overcome classical drug resistance, and achieve improved outcome in this presently incurable disease.

Id. at 2949-50 (citations omitted).

Around the time of publication of Hideshima 2000, Celgene announced that “the data suggests IMiDs(TM) may be beneficial in the treatment of multiple myeloma” and “additional studies of IMiDs(TM) are warranted.” Celgene Press Release (Oct. 30, 2000) [DEFS_POM_00001799-801]. Celgene also reported in this press release:

In addition, the data highlight that the IMiDs(TM) were active against myeloma cell lines that are resistant to other anti-myeloma agents. The IMiDs(TM) were found to have direct anti-tumor effects that include enhancement of multiple myeloma cell death (apoptosis) and cell cycle arrest. These compounds were also synergistic with other anti-myeloma agents in some of the cell lines studied.

“These results demonstrate evidence for direct activity of the IMiDs(TM) against human multiple myeloma cells,” said Kenneth C. Anderson, MD, Professor of Medicine in the Department of Adult Oncology at Dana-Farber Cancer Institute. “The results from these studies provide the framework for a new biologically-based treatment paradigm, using these agents either alone or in combination with conventional therapies, to overcome classical drug resistance and achieve improved outcome in this presently incurable disease.”

Hideshima 2000 qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 2000, which is more than a year before the earliest possible priority date.

10. Corral I

Corral I compares the effectiveness of thalidomide and thalidomide analogues or IMiDs, finding that these compounds inhibited TNF- α , IL-1b, and IL-6 and greatly increased IL-10

production by LPS-induced PBMC. Corral I at Abstract. Thalidomide was known to “lower[] plasma TNF- α protein levels and leukocyte TNF- α mRNA levels,” as well as “[]stimulate T cells in vitro . . . [which] increase[s] production of IL-2 and IFN- γ .” *Id.* at 380 (citation omitted). Corral compared these known properties of thalidomide to thalidomide analogues, which were reported to be “up to 50,000-fold more potent than thalidomide at inhibiting TNF- α production by PBMC in vitro.” *Id.* at 380-381 (see Table 1). Corral I references Muller, and the thalidomide analogs disclosed therein, identifying Corral I’s CI-A analog as Muller’s Compound 5a, i.e. pomalidomide (4-aminothalidomide). *Id.* at 381. Thus, Corral I discloses pomalidomide (compound CI-A) as a derivative of thalidomide. *Id.* at 381, Table 1. Corral I further discloses that compound CI-A is a more potent inhibitor of TNF- α than thalidomide. *Id.* In particular, compound CI-A (pomalidomide) had a TNF- α IC₅₀ of 10 nM, which was significantly smaller than the IC₅₀ of approximately 200 μ m for thalidomide in a TNF- α inhibition study. *Id.* In Corral I, pomalidomide “significantly inhibited” the multiple myeloma growth factor IL-6, and increased the anti-inflammatory cytokine IL-10, as compared to thalidomide. *Id.* at 381-82. Further, pomalidomide, and other class I analogues, “were potent costimulators of T cells and increased cell proliferation significantly in a dose-dependent manner,” as well as “augmented production” of T cell cytokines IL-2 and IFN- γ , as compared to thalidomide. *Id.* at 382-83. Corral I concludes that “[t]hese findings show that in addition to their strong anti-inflammatory properties, class I compounds [including pomalidomide] efficiently costimulate T cells, achieving both effects with 100 to 1000 times the potency of thalidomide.” *Id.* at 384. Thus, Corral I discloses that pomalidomide was known to be a particularly potent IMiD.

Around the time of publication of Corral I, Celgene reported that IMiDs had “improved safety profile in animal models” as well as greater potency than thalidomide. Celgene Press Release (July 7, 1999).

Corral I qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1999, which is more than a year before the earliest possible priority date.

11. Corral II

Corral II at figure 1 discloses the structure of three compounds as IMiDs; two of those structures match lenalidomide and pomalidomide so a POSA would know that the IMiDs include these two compounds. Corral II at I109, Fig. 1. Corral II discloses that the motivation for developing the IMiDs was to have “reduced or absent toxicities” as compared to thalidomide. Corral II at I107. Corral II discloses that “the more potent of these thalidomide analogues were found to be up to 50,000-fold more potent than thalidomide at inhibiting TNF α production by human PBMC stimulated by LPS in vitro.” *Id.* at I109. This reference further discloses that the IMiDs strongly inhibit LPS induced inflammatory cytokines: TNF- α , IL1 β , IL6 and IL12; strongly stimulate LPS induced anti-inflammatory cytokine IL10; strongly costimulate T cell activation; and do not inhibit PDE4. *Id.* The authors state that “[t]hese findings show that in addition to their strong anti-inflammatory properties, IMiDs efficiently costimulate T cells with 100 to 1000 times the potency of the parent drug [thalidomide].” *Id.* at I110.

Specifically, Corral II states that IMiDs “act as costimulators of T cells but are much more potent than the parent drug.” *Id.* at I107. In particular, Corral II discloses that “IMiDs, the non-PDE4 inhibitors, were potent costimulators of T cells and increased cell proliferation dramatically in a dose dependent manner.” *Id.* at I110 (citations omitted). Corral II discloses that “[w]hen T cells were stimulated by anti-CD3, thalidomide and IMiDs treatment caused a

significant stimulation of IL12 production,” and “also induced an up-regulation of CD40L on the surface of T cells.” *Id.* (citations omitted). Corral II also discloses that “IMiDs, when added to anti-CD3 stimulated T cells, also caused marked increases in the secretion of IL2 and IFN γ and induced the up-regulation of CD40L expression on T cells.” *Id.* (citations omitted).

Regarding the potential clinical application of IMiDs such as pomalidomide, Corral states:

IL12 has also been shown to exhibit potent anti-tumour activity in murine tumour models through various mechanisms including the stimulation of natural killer cell activity, activation of CD8 $^{+}$ cytotoxic T cells and increased IFN γ mediated anti-angiogenesis. Thalidomide has also recently been reported to exhibit antitumour activity through the inhibition of angiogenesis in vivo. However, this anti-angiogenic effect does not seem to be mediated by TNF α inhibition. Although these studies did not determine the mechanism of thalidomide’s antiangiogenic activity, it is conceivable that stimulation of IFN γ /IL12 levels may be at least partly responsible. One report indicates that thalidomide may have antiangiogenic activity in multiple myeloma in humans.

In summary, our recent findings that thalidomide and IMiDs preferentially costimulate CD8 $^{+}$ T cells and induce T cell dependent IL12 production suggest possible applications of these drugs in the control of viral infections or in boosting anti-tumour immunity.

Id. at I111 (citations omitted). Thus, Corral II discloses that IMiDs are potent costimulators of T-cells and cause significant stimulation of IL12 production and IL12 and IFN γ secretion, which suggests their use as anti-cancer agents to stimulate natural killer cell activity, boost anti-tumor immunity and inhibit angiogenesis.

Corral II qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(b), having published in 1999, which is more than a year before the earliest possible priority date.

12. Weber 2000

Weber discloses clinical efficacy of thalidomide on resistant multiple myeloma. Weber 2000 at 167a. Thalidomide was administered in combination with dexamethasone (20 mg/m 2)

on days 1-5 and 15-18, and responding patients were maintained on a maximally tolerated dose of thalidomide and dexamethasone on days 1-5 each month. *Id.* The authors report that “[r]esponses included 12 of 26 patients (46%) who were resistant to recent programs including high-dose dexamethasone and subsequent thalidomide alone, suggesting synergy.” *Id.* “Response rates were similar for 20 patients with primary refractory disease (55%) and 27 pts. with disease in refractory relapse (48%).” *Id.* The authors concluded that their results “confirm superior activity of thalidomide dexamethasone for resistant myeloma when compared with thalidomide alone.” *Id.*

Weber qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 2000, which is more than a year before the earliest possible priority date.

13. Rajkumar & Kyle

Rajkumar & Kyle disclose that thalidomide is part of standard therapy for relapsed myeloma even though that indication had not yet been approved by FDA. Rajkumar & Kyle at 3593. Rajkumar & Kyle disclose that higher doses of thalidomide (e.g., doses higher than 200 mg to 400 mg) are associated with high toxicity and may not yield better response rates than lower doses. *Id.* Rajkumar & Kyle disclose that the combination of thalidomide and dexamethasone may act synergistically because a Mayo Clinic study using this combination as an initial therapy for previously untreated myeloma indicate promising activity with a response rate of over 75%. *Id.* at 3594. Rajkumar & Kyle also disclose that other thalidomide derivatives with reduced side effects are being developed and tested in clinical trials such as CC-5013 (i.e. lenalidomide). *Id.*

Rajkumar & Kyle qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having published in August 2001.

14. Kropff

Kropff discloses the combination of thalidomide (escalating doses of 100 to 400 mg/day) and dexamethasone (20 mg/m²/day) administered in a month-long cycle to treat primary refractory or relapsed multiple myeloma. Kropff at 168a. Dexamethasone was administered on days 1-4, 9-12, and 17-20. *Id.*

Kropff qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 2000, which is more than a year before the earliest possible priority date.

15. Klausner I

Klausner I discloses the use of thalidomide (300 mg/day) daily for 21 days followed by a seven-day washout period in patients with HIV-1. Klausner I at 248. Klausner I qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1996, which is more than a year before the earliest possible priority date.

16. Klausner II

Klausner II discloses the treatment of tuberculosis patients with 300 mg/day of thalidomide for a 14-day cycle followed by a 7-day washout period at the end of a cycle of thalidomide treatment. Klausner II at 221. Klausner II qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1996, which is more than a year before the earliest possible priority date.

17. June Market Letter

June Market Letter discloses the use of the immunomodulatory drug lenalidomide (also known as Revimid or Revlimid or CDC501), an orally available analog of thalidomide, as a promising treatment for multiple myeloma. June Market Letter at 1. It also discloses that Revlimid is designed to be more potent and have demonstrated a better safety profile in clinical

trials than thalidomide. *Id.* June Market Letter describes the latest clinical trial involving administering 5, 10, 25, and 50 mg/day of lenalidomide to 20 patients, with 13 of those patients showing evidence of disease stabilization. *Id.*

June Market Letter qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. §§ 102(a) and/or 102(b), having published in June 2001.

18. October Market Letter

October Market Letter discloses the use of the immunomodulatory drug (IMiD™) lenalidomide (also referred to as Revimid), an orally available analog of thalidomide, as a promising treatment for multiple myeloma. October Market Letter at 1. The publication discloses that “up to 60% of patients enjoy a clinical response to the drug.” *Id.* October Market Letter discloses that IMiDs are designed to be more potent and have demonstrated a better safety profile in clinical trials than the parent compound thalidomide. *Id.*

October Market Letter qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. §§ 102(a) and/or 102(b), having published on October 1, 2001.

19. Hideshima 2001

Hideshima 2001 discloses treatment of human multiple myeloma cells with PS-341 (i.e. bortezomib). Hideshima 2001 at 3071. Hideshima 2001 teaches that “[p]roteasome inhibitors represent a novel potential anticancer therapy” based on a study that “demonstrate[s] that the proteasome inhibitor PS-341 directly inhibits proliferation and induces apoptosis of human MM cell lines and freshly isolated patient MM cells. . . .” Hideshima 2001 at 3071. Specifically, Hideshima “examined the effects of PS-341 on human MM [multiple myeloma] cell lines, freshly isolated patient MM cells, as well as MM cells adherent to BMSCs.” *Id.* Hideshima additionally disclosed that “PS-341 is nearly completing Phase I testing in humans, with an acceptable toxicity profile, and will soon be evaluated for efficacy in Phase II clinical trials.” *Id.*

Therefore, PS-341 was shown to have an acceptable toxicity profile in Phase I clinical trials and PS-341 was shown to inhibit the growth of multiple myeloma cells.

Hideshima 2001 qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 2001, which is more than a year before the earliest possible priority date.

20. WO 98/03502

WO 98/03502 is titled “Substituted 2-(2,6-dioxopiperidin-3-yl)phthalimides and -1-oxoisindolines and Method of Reducing TNF-Alpha Levels.” WO 98/03502 discloses the use of pomalidomide for the treatment of cancer. For example, WO 98/03502 discloses 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisindoline, i.e., pomalidomide, and its use for “[d]ecreasing TNF- α levels and/or increasing cAMP levels thus constitutes a valuable therapeutic strategy for the treatment of many inflammatory, infectious, immunological, and malignant diseases. These include but are not restricted to ... oncogenic or cancerous conditions.” WO 98/03502 at 7:23-24, 5:20-26. WO 98/03502 also discloses an oral dosage of 1 to 100 mg of pomalidomide per unit dosage. *Id.* at 11:19-20. WO 98/03502 has the same, or substantially the same disclosures as prior art patent U.S. Patent No. 6,281,230, titled “Isoindolines, Method of Use, and Pharmaceutical Compositions,” which is listed in the Orange Book for Revlimid.

WO 98/03502 qualifies as prior art to the '262, '939, '428, and '427 patents under at least 35 U.S.C. § 102(b), having published in 1998, which is more than a year before the earliest possible priority date.

21. Marriott 2001

Marriott 2001 discloses that a structural analog of thalidomide, 3-aminothalidomide or pomalidomide, demonstrated “[c]linical activity in vivo is attributed to the wide ranging immunological and non-immunological properties,” including “anti-TNF- α , T-cell co-

stimulatory, anti-angiogenic activities and also direct antitumour activity.” Marriott 2001 at 675, 677 (referencing Muller), 679 Table 2. Marriott 2001 teaches that “[t]he IMiDs are a class of thalidomide analogues that potently inhibit TNF- α and IL-1 β and stimulate IL-10 formation in LPS stimulated human PBMC.” *Id.* at 679. Marriott 2001 discloses that “[t]halidomide analogues also clearly possess enhanced activity over the parent compound in their relative effects on the growth inhibition of chemoresistant human myeloma cells. IMiD analogues were far more effective than both thalidomide and SelCID [selective cytokine inhibitory drug] analogues with IC₅₀ values of 0.1 - 1.0 μ M. Furthermore, their effect appeared to be IL-6 dependent.” *Id.* at 679. Marriott 2001 teaches that “unpublished preliminary studies suggest that both SelCID and IMiD analogues demonstrate improved anti-angiogenic activity in both rat and human *in vitro* systems and this is clearly an area of considerable interest.” *Id.* at 679. Moreover, Marriott 2001 discloses that lenalidomide (i.e. CDC-501) is under clinical development and was advanced to Phase I/II clinical trials for relapsed and refractory multiple myeloma in humans. *Id.* at 679. Marriott 2001 concludes that “the potential of these [IMiD] compounds span such diverse activities as anti-TNF- α action, T-cell costimulation (suggesting possible use in the augmentation of vaccination regimens), anti-angiogenesis and direct antitumour effects.” *Id.* at 680.

Marriott 2001 qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having been published in July 2001.

22. D'Amato 2001

D'Amato discloses that pomalidomide (3-aminothalidomide) inhibits multiple myeloma cell growth and reports that “[a]lthough thalidomide does not have any direct effect on myeloma cells *in vitro*, 3-aminothalidomide very potently inhibits myeloma cell growth.” D'Amato 2001 at 599.

D'Amato discloses that "Vacca *et al.* in 1994 demonstrated increased bone marrow angiogenesis in active multiple myeloma," and "[i]n 1995, they proposed the use of (as yet unavailable) antiangiogenic therapy in multiple myeloma." D'Amato 2001 at 598. D'Amato discloses that "[i]n addition to antiangiogenesis, thalidomide has a second mechanism of action that may be relevant in multiple myeloma." *Id.* In particular, since "[t]halidomide has been shown to downregulate tumor necrosis factor-alpha (TNF- α) by destabilizing its message," and "[s]ince TNF- α has been shown to be a growth and survival factor for myeloma cells, disruption of TNF- α expression might be expected to result in cessation of cell growth and even cell death." *Id.* (citations omitted). D'Amato states that "[a]s a result of this work demonstrating that thalidomide is an inhibitor of TNF- α , we set out to determine whether thalidomide's antiangiogenic effects are mediated by TNF- α ," but observed that other TNF- α inhibitors did not inhibit blood vessel formation, which "is evidence that TNF- α does not play a role in the angiogenic response." *Id.* D'Amato states that "[a]nother way to approach this question is to determine whether there is a correlation between TNF- α inhibition and antiangiogenesis in thalidomide derivatives." *Id.* D'Amato discloses that "[i]f thalidomide blocks angiogenesis by regulating TNF- α , one would expect 3-aminothalidomide to be a more effective angiogenesis inhibitor than thalidomide, since the former compound is a 15,000-fold more potent TNF- α inhibitor than thalidomide." *Id.* at 599. However, D'Amato "found that 3-aminothalidomide and thalidomide inhibit angiogenesis to a similar extent." *Id.* Thus, D'Amato concludes that "we have failed to find any correlation between thalidomide's effects on TNF- α and angiogenesis." *Id.*

D'Amato discloses that "[w]e have, however, observed a remarkable property of 3-aminothalidomide," namely that "[a]lthough thalidomide does not have any direct effect on

myeloma cells in vitro, 3-aminothalidomide very potently inhibits myeloma cell growth.” *Id.* D’Amato discloses that “[t]he in vitro sensitivity of some myeloma cells to 3-aminothalidomide raises the very interesting possibility that thalidomide analogs may be capable of inhibiting not only blood vessels, but also tumor cells directly, thus resulting in better clinical responses.” *Id.*

Regarding the mechanism of action, D’Amato tested other TNF- α inhibitors for the ability to act directly on multiple myeloma cells, and based on the fact that others failed to inhibit myeloma cell growth, “conclude[d] that 3-aminothalidomide does not inhibit myeloma cell growth by inhibiting TNF- α secretion.” *Id.* D’Amato discloses that “even though we believe [TNF- α] is unlikely to play a major role in either angiogenesis or myeloma cell inhibition . . . reports that both thalidomide and 3-aminothalidomide upregulate interferon-gamma are of interest [because w]e have found that a continuous low-dose infusion of interferon-gamma can produce almost 100% suppression of angiogenesis in the mouse eye assay.” *Id.* (citation omitted). D’Amato states that:

This occurs via the induction of inducible protein-10 (IP-10), a direct angiogenesis inhibitor. In addition to interferon-gamma, both drugs have been shown to upregulate IL-10, a cytokine whose antiangiogenic properties have recently been described. These results suggest that both thalidomide and 3-aminothalidomide may inhibit angiogenesis, at least in part, by upregulating IP-10 via interferon-gamma and/or IL-10.

Id. (citations omitted). D’Amato further discloses that “thalidomide has been reported not to affect IL-6 levels, whereas 3-aminothalidomide has been reported to downregulate IL6.” *Id.* at 600. Moreover, “[s]ince IL-6 is an important autocrine and paracrine growth factor for myeloma, this suggests the possibility that 3-aminothalidomide may directly inhibit myeloma cells through a suppression of IL-6.” *Id.*

Thus, D’Amato discloses that pomalidomide inhibits angiogenesis and multiple myeloma cell growth, whereas thalidomide only inhibits angiogenesis. Accordingly, D’Amato concludes

that “[t]his analog offers great promise for the treatment of multiple myeloma through its combined antiangiogenic and antiproliferative activities.” *Id.*

D’Amato qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. §§ 102(a) and/or 102(b), having published in December 2001.

23. Aviles

Aviles discloses that dexamethasone is effective against refractory multiple myeloma when administered on days 1 to 4 of a 21-day cycle at a dose of 40 mg/m². Aviles at 23. Aviles reported a response rate of 83% for patients with refractory multiple myeloma, and that toxicity of this dosing schedule was mild. *Id.*

Aviles qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(b), having published in 1999, which is more than a year before the earliest possible priority date.

24. Thalomid Product

The Thalomid Product was commercially available since October 1, 1998. *See* 1998 Thalomid Label; FDA (July 16, 1998), *FDA Approves Thalidomide for Hansen’s Disease Side Effect, Imposes Unprecedented Restrictions on Distribution* (FDA Talk Papers); Celgene (July 17, 1998), *Celgene Announces FDA Clears Thalidomide For Sale in U.S.* (Press Release); Celgene (February 24, 1999), *Celgene to Collaborate With the National Cancer Institute in a Study of Thalidomide and Radiation Therapy to Treat Glioblastoma* (Press Release); Celgene’s 10-K for the fiscal year ending December 31, 1998. The FDA approved Thalomid to be indicated for the treatment of multiple myeloma in May 2006. *See* 2006 Thalomid Label; FDA Approval Letter for MM in Thalomid.

The 1998 Thalomid Label discloses that thalidomide is indicated for acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL) and is also

indicated for maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence. 1998 Thalomid Label at 8. The 1998 Thalomid Label further discloses that “[f]or an episode of cutaneous ENL, THALOMID dosing should be initiated at 100 to 300 mg/day, administered once daily.” *Id.* at 18. “In patients with a severe cutaneous ENL reaction, or in those who have previously required higher doses to control the reaction, THALOMID dosing may be initiated at higher doses up to 400 mg/day once daily.” *Id.* Thalomid was available in 50 mg capsules for oral administration, and these capsules included several inactive ingredients. *Id.* at 5. The 2003 Thalomid Label states that the inactive ingredients for Thalomid included pregelatinized starch and magnesium stearate. 2003 Thalomid Label at 4.

Thalomid qualifies as 35 U.S.C. § 102(b) prior art to the ’262, ’939 and ’428 patents, because it was made, used, offered for sale and sold in the United States in 1998, which is more than a year before the earliest possible priority date.

25. Dimopoulos

Dimopoulos discloses the use of thalidomide (escalating doses of 200 to 400 mg/day) in combination with dexamethasone (20 mg/m²/day) as a “salvage treatment for heavily pretreated patients with multiple myeloma” and that thalidomide in combination with dexamethasone can be used to treat patients with refractory multiple myeloma. Dimopoulos at 991. Dimopoulos further discloses that dexamethasone was administered daily for four days on days 1-4, 9-12, 17-20, followed by monthly dexamethasone for four days. *Id.* Moreover, Dimopoulos discloses that “Hideshima et al. recently showed that thalidomide enhances the antimyeloma activity of dexamethasone *in vitro*. All these observations indicate that there is a synergistic effect between thalidomide and dexamethasone.” *Id.* at 994.

Dimopoulos qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a) or § 102(b), having published in 2001, and accepted for publication on April 11, 2001.

26. 2000 Abstracts

The 2000 Abstracts disclose the anti-myeloma properties of IMiDs including pomalidomide. Abstract #2485 discloses *in vitro* studies of thalidomide and its analogue IMiD1 on gene transcription in multiple myeloma cell line ARP-1. The study concludes “that the efficiency of thalidomide [and IMiD1] in the treatment of myeloma may be linked to modulation of genes with the myeloma cell itself, rather than antiangiogenic effects.” 2000 Abstracts at 579a. Abstract #2486 discloses *in vitro* studies of IMiDs and concludes that “[b]ased on their striking direct growth-inhibitory and potential anti-angiogenic effects, IMiDs appear to be promising for the treatment of refractory MM.” *Id.* Abstract #2487 discloses *in vitro* studies of the effect of IMiD1 on the cell cycle of multiple myeloma cell lines (HS-Sultan and MM. IS). *Id.* The study further discloses that “[d]examethasone and 5 FU when combined with IMiD1, increased the cell cycle arrest in HS-Sultan to 90% and 51%, respectively, which was 30% more than the effect of each drug alone.” *Id.* The study concludes that “[t]hese experiments demonstrate that the thalidomide analog, IMiD1 in combination with other drugs such as dexamethasone can cause greater growth arrest than these drugs alone.” *Id.* Moreover, Abstract #3617 concludes that “*in-vitro* and *in-vivo* data suggest that Thal may mediate its anti-MM effect by modulating NK cell number and function.” *Id.* at 837a. *See also* Celgene Press Release (Dec. 5, 2000) [DEFS_POM_00001823-824].

The 2000 Abstracts qualify as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having been presented publicly at the 42nd annual meeting of the American

Society of Hematology in San Francisco on December 1-5, 2000 and published on November 16, 2000.

27. Davies

Davies discloses that thalidomide and immunomodulatory derivatives (i.e. IMiD1, IMiD2, and IMiD3) may be used to treat multiple myeloma. A POSA would know that IMiD3 is lenalidomide. Tsenova 2002 cites to the Davies (reference 9) and discloses that IMiD3 is indicated to be α -3-aminophthalimido-glutarimide (i.e. pomalidomide). Tsenova 2002 at 1889. However, Tsenova 2002 incorrectly identified IMiD3 as α -3-aminophthalimido-glutarimide (i.e., pomalidomide), which was corrected by way of an erratum which identifies IMiD3 as [3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione]” (i.e., lenalidomide). *See* Tsenova Erratum.

Davies discloses that “[r]ecent reports of increased bone marrow angiogenesis in multiple myeloma (MM), coupled with the known antiangiogenic properties of thalidomide (Thal), provided the rationale for its use to treat patients with MM.” Davies at 210. Davies states “[h]owever, there was no correlation of bone marrow angiogenesis with response to treatment, suggesting that Thal may not mediate its anti-MM activity through its antiangiogenic effects alone.” *Id.* Davies discloses that although thalidomide’s “mechanism of action was initially thought to be through the inhibition of cytokine production by monocytes, particularly tumor necrosis factor α . . . , more recent studies have suggested that Thal may also act as a costimulatory signal to T cells, inducing T-cell proliferation associated with interferon γ (IFN- γ) and interleukin 2 (IL-2) production.” *Id.* (citations omitted). Davies reports that “[n]ew analogues of Thal have been produced that are . . . more potent inducers of T-cell proliferation

with IFN- γ and IL-2 secretion and inhibitors of IL-1 β and IL-6 secretion from PBMCs; hence, these drugs have been named IMiDs.” *Id.* (citations omitted).

Davies “investigated the immunomodulatory effects of Thal and 3 potent IMiDs in MM.” *Id.* Davies states that “[a]lthough these drugs induce the proliferation of MM patient T cells as well as IFN- γ and IL-2 secretion in vitro, these T cells are not cytotoxic and do not lyse autologous MM cells.” *Id.* However, Davies conducted a series of experiments which “demonstrate that these drugs markedly enhance in vitro NK-cell-mediated lysis of both MM cells lines and autologous patient MM cells.” *Id.* at 210-11. Davies teaches that IL-2–primed peripheral blood mononuclear cells (PBMCs) treated with Thal/IMiDs demonstrated significantly increased lysis of MM cell lines. *Id.* IMiD1 showed the highest percentage of cell lysis when compared to thalidomide, IMiD3 and IMiD2. *Id.* at 210, 214, Fig. 6. Moreover, Davies states that “in vivo there is an increase in NK cell number in patients responding to Thal therapy.” *Id.* at 211. Davies states that “[m]easurement of cytokines in the plasma from patients also showed that the decrease in paraprotein and the increase in NK cells was accompanied by an increase in IL-2 and IFN- γ secretion,” which “suggest[s] that the immunomodulatory effects of Thal mediate, at least in part, its anti-MM activity.” *Id.* at 216. In particular, “the direct effect of Thal on T cells results in an increase in IL-2 and IFN- γ secretion, which augments NK cell number and function.” *Id.*

Davies discloses that thalidomide and IMiDs (i.e. IMiD1, IMiD2 and IMiD3) act directly on MM cells through “dose-dependent inhibition of proliferation even in MM cell lines and patient MM cells resistant to conventional chemotherapy, and they add to the effect of dexamethasone (Dex).” *Id.* at 210. Davies concludes that “[t]hese data therefore suggest that Thal and the IMiDs, in addition to their direct inhibition of MM cell proliferation and survival

and antiangiogenic effects in the bone marrow (BM), may also induce NK cell anti-MM immune responses.” *Id.* at 211 (citations omitted). Davies further concludes that “our results suggest that Thal and new analogues may not only be useful in the treatment of refractory/relapsed disease, but also be effective in the maintenance of minimal residual disease after transplantation by enhancing NKcell-mediated anti-MM cell immunity.” *Id.* at 216.

Davies qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(a) or § 102(b), having been submitted in December 2000, accepted for publication in March 2001, and published in July 2001.

28. Fujita

Fujita discloses that based on *in vitro* studies in murine macrophage-like cell lines, thalidomide and structural analogs of thalidomide (e.g. IMiD1, IMiD2, and IMiD3) inhibit LPS induction of Cox-2 and PGE2 synthesis similar to, or greater than, that of thalidomide. Fujita at 3353, Fig. 7.

Fujita qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(a) or § 102(b), having been received on May 30, 2001 and publishing in November 2001.

29. Stirling

Stirling discloses that Phase I/II studies of lenalidomide (i.e. CDC501) in multiple myeloma were in progress. Stirling at 602. Stirling further discloses that lenalidomide was safely administered to volunteers in single doses of 50 to 400 mg. *Id.*

Stirling qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. §§ 102(a) and/or 102(b), having published in December 2001.

30. Richardson I

Richardson discloses that in phase I studies, lenalidomide (i.e. CC-5013) had favorable safety profiles in human volunteers and “anti-tumor activity and acceptable toxicity in p[atients]

with relapsed and refractory MM....” Richardson I at 775a. Richardson I further discloses that lenalidomide was given orally for up to 4 weeks at doses of 5 mg/day to 50 mg/day. *Id.*

Richardson I qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. §§ 102(a) and/or 102(b), having published in November 2001.

31. Gupta

Gupta discloses that pomalidomide (i.e. IMiD1-CC4047) has anti-tumor effects in human multiple myeloma cells. Gupta at 1950. Gupta states that “thalidomide (100 μ M) and its immunomodulatory analog IMiD1-CC4047 [i.e. pomalidomide] (1 μ M) decreased the upregulation of IL-6 and VEGF secretion in cultures of BMSCs, MM cells and co-cultures of BMSCs with MM cells” demonstrating “the importance of stromal–MM cell interactions in regulating VEGF and IL-6 secretion, and suggest additional mechanisms whereby thalidomide and IMiD1-CC4047 act against MM cells in the BM milieu.” *Id.* Gupta further discloses the “known ability of thalidomide and immunomodulatory drug (IMiD1-CC4047) to modulate cytokines and inhibit angiogenesis...” *Id.* at 1955. Gupta identifies pomalidomide as “more potent” than thalidomide, and observes that it “does act directly to induce G1 growth arrest and apoptosis in HS-Sultan, RPMI, U266 and MM2 cells.” *Id.* at 1959.

Gupta qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a) or § 102(b), having been received in January 2001, accepted for publication in July 2001, and published in 2001.

32. Dredge 2001

Dredge 2001 discloses that pomalidomide (i.e. CC-4047/ACTIMID) has anti-tumor effects in mice. Dredge 2001 at Abstract, 4918-19. Dredge 2001 “found that the presence of CC-4047 during the priming phase strongly enhanced antitumor immunity in the vaccinated

group, and this correlated with protection from subsequent live tumor challenge.” *Id.* at Abstract.

Dredge 2001 qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(a), having been received for publication in November 2001, accepted for publication in March 2002, and published in 2002.

33. Dredge 2002

Dredge 2002 discloses that lenalidomide (i.e. IMiD-1 or Revimid) inhibited tumor growth *in vivo* and was “under phase I/II clinical investigation in the treatment of end stage cancer in patients (Marriott *et al*, 2002).” Dredge 2002 at Abstract, 1172. Dredge 2002 states that “[f]or *in vivo* treatment experiments, mice were treated daily with 10 or 50 mg kg⁻¹ IMiD-1.” *Id.* at 1167 Dredge 2002 also discloses that “[t]he effects of SelCIDs and IMiDs in this study provide further evidence of the clinical potential of these novel compounds as anti-tumor drugs. IMiD analogues have been shown to induce myeloma cell growth arrest *in vitro* (Hideshima *et al*, 2000).” *Id.* at 1171-1172.

Dredge 2002 qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. §§ 102(a) and/or 102(b), having been received for publication in February 2002, accepted for publication in August 2002, and published in 2002.

34. Dredge 2003

Dredge 2003 discloses that pomalidomide (i.e. CC-4047, Actimid) “is currently under investigation in phase I/II and II trials for multiple myeloma and prostate cancer.” Dredge 2003 at Abstract. Dredge 2003 further discloses that pomalidomide “has recently been found to possess an acceptable safety profile in a phase I trial for relapsed/refractory multiple myeloma.” *Id.* at 333. Dredge 2003 concludes that “[t]he enhanced efficacy and lower side-effect profiles of the analogs in comparison to thalidomide make the use of these agents very attractive as novel

anti-cancer agents.” *Id.* at Abstract. Dredge 2003 also discloses studies that show IMiDs, including pomalidomide and lenalidomide (i.e. CC-4047 and CC-5013, respectively), where IMiD activity was able to potentiate dexamethasone in anti-myeloma therapy. *Id.* at 333.

Dredge 2003 qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(a), having been received for publication in February 2003 and accepted for publication in March 2003.

35. Mitsiades

Mitsiades discloses that pomalidomide (i.e. IMiD1, CC4047, CDC394, Actimid) and lenalidomide (i.e. IMiD3, CC5013, CDC501, Revimid) have anti-MM effects in human cells. Mitsiades at 4526-27, 4529. Mitsiades further discloses that IMiDs potentiate the activity of dexamethasone. *Id.* at 4525. For example, the Mitsiades Abstract states:

[W]e have shown that Thal and its immunomodulatory analogs (IMiDs) directly induce apoptosis or growth arrest of MM cells, alter adhesion of MM cells to bone marrow stromal cells, inhibit the production of cytokines (interleukin-6 and vascular endothelial growth factor) in bone marrow, and stimulate natural killer cell anti-MM immunity. In the present study, we demonstrate that the IMiDs trigger activation of caspase-8, enhance MM cell sensitivity to Fas-induced apoptosis, and down-regulate nuclear factor (NF)-κB activity as well as expression of cellular inhibitor of apoptosis protein-2 and FLICE inhibitory protein. IMiDs also block the stimulatory effect of insulin like growth factor-1 on NF-κB activity and potentiate the activity of TNF-related apoptosis-inducing ligand (TRAIL/Apo2L), dexamethasone, and proteasome inhibitor (PS-341) therapy. These studies both delineate the mechanism of action of IMiDs against MM cells in vitro and form the basis for clinical trials of these agents, alone and coupled with conventional and other novel therapies, to improve outcome in MM.

Mitsiades further states:

[O]ur findings delineate the intracellular signaling mechanisms whereby IMiDs induce MM cell apoptosis. They also show that the IMiDs potentiate the anti-MM activity of Fas cross-linking, TRAIL/Apo2L, Dex, and the proteasome inhibitor PS-341, providing the framework for derived clinical trials in MM.

Id. at 4529.

Mitsiades qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having been accepted for publication in January 2002 and publishing in June 2002.

36. Lentzsch 2003

Lentzsch 2003 discloses the anti-tumor activity of IMiD1 and IMiD3 in mice. Lentzsch 2003 at 42. Lentzsch 2003 furthers discloses that, “[i]mportantly, IMiD1 completely inhibited tumor development. These data suggest that the IMiDs can effectively treat a lower burden of tumor cells,” and “even when treatment was initiated after the tumor was established, we observed an almost complete and sustained remission of tumors until day 45 of IMiD1 treatment in all animals.” *Id.* at 44. In addition, Lentzsch 2003 discloses that thalidomide and IMiDs, including pomalidomide and lenalidomide, enhance the anti-MM activity of dexamethasone. *Id.* at 41.

Lentzsch 2003 qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having been received for publication on May 7, 2002 and publishing in 2003.

37. Raje

Raje discloses that thalidomide analogues “have increased potency and have demonstrated efficacy and reduced toxicity in phase I and II clinical studies.” Raje at 635. Raje also discloses administering lenalidomide to patients with relapsed and refractory multiple myeloma, and that the maximum tolerated dose for lenalidomide (i.e. CC5013) is 25 mg/day. Raje at 638. Raje qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having published in 2002.

38. Richardson II

Richardson II discloses the use of lenalidomide (i.e. CC-5013) to treat relapsed and refractory relapsed multiple myeloma in humans. Richardson II at 3063. Richardson II further discloses that “[i]n 24 evaluable patients, no dose-limiting toxicity (DLT) was observed in

patients treated at any dose level within the first 28 days,” and “[i]mportantly, no significant somnolence, constipation, or neuropathy has been seen in any cohort.” *Id.* Richardson II also discloses the maximal tolerated dose of lenalidomide to be 25 mg/day. *Id.* In addition, Richardson II states that “our preclinical data suggest that Dex also enhances anti-MM activity of CC-5013.” *Id.* at 3067.

Richardson II qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having been submitted in April 2002 and publishing in November 2002.

39. Richardson III

Richardson III discloses the chemical structure for pomalidomide and lenalidomide, and notes that the “emergence of orally active thalidomide derivatives with considerable promise for improved efficacy and less toxicity also provide an exciting platform for the future treatment of this otherwise deadly disease.” Richardson III at Fig. 1, 126. Richardson III further discloses that thalidomide and IMiDs (e.g., pomalidomide and lenalidomide) enhance the anti-tumor activity of dexamethasone. *Id.* at 118.

Richardson III qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having been received in December 2001, accepted for publication in January 2002, and published in 2002.

40. Marriott 2002

Marriott 2002 discloses that “Thd and its co-stimulatory IMiD analogues, in particular CC-4047 [i.e. CC-4047/Actimid] and CC-5013 [i.e. CC-5013/Revimid], are currently being assessed in the treatment of patients with advanced multiple myeloma and patients with advanced solid tumours.” Marriott 2002 at 76. It further discloses that pomalidomide (i.e. CC-4047/Actimid) had profound immunostimulatory effects orally at 5 mg/day in patients with advanced multiple myeloma. *Id.* at 83. Marriott 2002 compares pomalidomide to lenalidomide

(i.e. CC-5013/Revimid) and discloses that immunostimulatory effects were seen in advanced cancer patients at weeks 1–3 after commencing lenalidomide at a dose of up to 25 mg/day. *Id.*

Marriott 2002 qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having been accepted for publication in June 2002.

41. Schey I

Schey I discloses the use of pomalidomide (i.e. CC-4047) in humans for the treatment of multiple myeloma. Specifically, Schey I discloses a “Phase I dose escalation study in relapsed/refractory multiple myeloma designed to identify the maximum tolerated dose (MTD) and evaluate the safety of CC-4047 when given orally for 4 weeks [28-days]. Patients were enrolled in cohorts of 3 at each dose level: 1 mg/day, 2mg/d, 5mg/d and 10mg/d.” Schey I at 98. Schey I further discloses that, based on preliminary results, the MTD of pomalidomide was 5 mg/day in the 28-day study. *Id.* This disclosure is similar to the disclosure in the '262, '939 and '428 patents.

Schey I qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having been presented publicly at the 31st Annual Meeting of the International Society for Experimental Hematology on July 5-9, 2002 and publishing in June 2002.

42. Schey II

Schey II discloses a phase I study of pomalidomide (i.e. CC-4047) in relapsed/refractory multiple myeloma. Schey II at 296. Schey II further discloses that “[p]atients were studied at escalating doses of the drug in cohorts of three patients starting at 1 mg per day and increasing according to response to 10 mg per day.” *Id.* Moreover, Schey II discloses that the success of thalidomide as a single agent in advanced myeloma prompted investigation of the combination of thalidomide with dexamethasone with initial results being positive suggesting synergy between the two agents. *Id.* at 295. Schey II reports that analogues, including pomalidomide,

have been developed to “improve efficacy and reduce toxicity,” and that two in particular, including pomalidomide, are in clinical development with promising results. *See* Schey II at 295. Schey II describes the clinical studies of pomalidomide in patients with relapsed or refractory myeloma and reports that the results are “very encouraging.” *Id.* at 296.

Schey II qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having been received in August 2002 and publishing in October 2002.

43. Schey III

Schey III discloses a phase I study which demonstrates the safety and efficacy of pomalidomide (i.e. CC-4047) in relapsed or refractory multiple myeloma. Schey III at 3269. Schey III discloses that the MTD of pomalidomide orally was 2 mg/day in the 4 week (28 day) phase I study. *Id.*

Schey III qualifies as prior art to the '262, '939, '428 and '427 patents under at least 35 U.S.C. § 102(a), having been submitted in October 2003 and publishing in August 2004.

44. Celgene Annual Report 1999

Celgene Annual Report 1999 discloses that Celgene completed Phase I safety trials for two lead IMiDs, which were found to be well-tolerated in healthy human volunteers. Celgene Annual Report 1999 at 2. It further shows that pomalidomide and lenalidomide (i.e. CC-4047 and CC-5013, respectively) were the two lead IMiDs. *Id.* at 4, 12-13. Celgene Annual Report 1999 further discloses that pomalidomide and lenalidomide “were found to be far more potent TNF α inhibitors than thalidomide,” and that the compounds’ potential anti-cancer properties had been confirmed in animal studies. *Id.* at 12-13.

Celgene Annual Report 1999 qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1999, which is more than a year before the earliest possible priority date.

45. Celgene Press Releases

In press releases since September 3, 1998, Celgene has been publicizing the beneficial properties of IMiDs as well as their similarities to and improvements over thalidomide for treatment of various diseases and disorders, including multiple myeloma. [DEFS_POM_00001799-870]. For example, on September 3, 1998, Celgene announced that IMiDs “are structural derivatives of thalidomide” that are “up to 100,000 times more potent than thalidomide in inhibiting the production of TNF-alpha” and “may have considerably lower teratogenic potential than the parent compound thalidomide.” Similarly, Celgene announced on July 7, 1999 that it had selected an IMiD compound “for evaluation in initial (Phase I) clinical trials,” and that IMiDs afford the “same or improved immunotherapeutic effects as thalidomide but with a greatly reduced toxicity profile.” Celgene also announced clinical studies of thalidomide with patients having multiple myeloma on December 6, 1999. Celgene also announced on February 29, 2000 that its two lead IMiDs were found to be “well-tolerated in healthy human volunteers” when IMiDs were administered in a “single ascending dose,” and that lenalidomide (or IMiD CDC-501) would be initiated with Phase I/II clinical studies in multiple myeloma patients. Celgene announced on December 5, 2000, that several studies showed IMiDs “may be beneficial in the treatment of multiple myeloma.” On May 8, 2001 and June 7, 2001, Celgene announced interim data in Phase I/II trials of lenalidomide in multiple myeloma patients, dosing of lenalidomide of 5 mg, 10 mg, 25 mg and 50 mg per day, and administration of lenalidomide to patients with refractory multiple myeloma with encouraging results. On August 28, 2001, Celgene announced that the ’517 patent “covers the active ingredient of Revimid and therapeutic uses of this and other IMiDs,” and that U.S. Patent No. 6,281,230 also “covers use of Revimid... to treat cancer...both as a single agent and in combination with other therapies.” On October 8, 2001, Celgene announced it had received an orphan drug designation from the FDA

for Revimid for multiple myeloma. On November 13, 2001, Celgene announced that pomalidomide (or Actimid) had been found to be “well-tolerated in a single blind, placebo-controlled ascending dose Phase I trial” and that it was currently being evaluated for refractory multiple myeloma in Phase I/II trials. On July 8, 2002, Celgene announced that pomalidomide (or Actimid) had “demonstrated anti-tumor activity in [patients with] multiple myeloma and has an acceptable toxicity profile.” These press releases are prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(a) or § 102(b).

46. Lentzsch 2001

Lentzsch 2001 discloses that S-3APG [i.e. pomalidomide] has marked anti-MM activity. Lentzsch 2001 at 473a. Lentzsch 2001 further discloses that all pomalidomide treated mice with MM IR tumors achieved complete remission and remained tumor free until day 100. *Id.* Lentzsch 2001 teaches that pomalidomide has an anti-tumor effect *in vivo* on RPMI-8226 MM cell lines, which are resistant to S-3APG *in vitro*. *Id.* Lentzsch 2001 further discloses that “S-3APG inhibited the proliferation of MM I.S cells... in coculture with bone marrow stroma cells (BMSC). There were no signs of toxicity on BMSC or human umbilical endothelial cell proliferation, nor on hematopoietic progenitor cell (CD3-I-) colony formation.” *Id.* Lentzsch 2001 concludes that “[o]ur results show that S-3APG could be a potent new drug for the treatment of MM. S-3APG exerts its anti-myeloma activity by a combination of direct dose-dependent anti-proliferative effect on MM cell lines resistant to conventional therapy and by inhibition of angiogenesis *in vivo*. Thus, S-3APG demonstrates superior *in vivo* anti-MM-activity compared to Thal and induces sustained complete tumor remission *in vivo*, without evidence of toxicity.” Lentzsch 2001 further teaches that the studies provide the framework for phase I trials of S-3APG in MM. *Id.*

Lentzsch 2001 qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in November 2001, which is more than a year before the earliest possible priority date.

47. Lentzsch 2002

Lentzsch 2002 teaches that “[t]halidomide has recently been shown to be useful in the treatment of multiple myeloma and may also be useful in the treatment of other hematological malignancies.” Lentzsch 2002 at 2300. Lentzsch 2002 identifies a derivative of thalidomide, S-3APG (i.e. pomalidomide), which exhibited dual activity against B-cell neoplasias, and was able to “directly inhibit the proliferation of myeloma ... *in vitro* without showing toxicity to normal bone marrow stromal cells or hematopoietic progenitor cells.” *Id.* Lentzsch 2002 teaches that S-3APG was S-3-[3-amino-phthalimido]-glutarimide], which is pomalidomide. *Id.*

Lentzsch 2002 discloses that “*in vivo*, S-3APG [i.e. pomalidomide] treatment of drug resistant myeloma cell tumors in mice was able to produce complete and sustained regressions without any observed toxicity” and “inhibited angiogenesis more potently than thalidomide.” *Id.* Lentzsch 2002 further discloses that they “studied MM.1R cells resistant to dexamethasone to determine whether there was cross-resistance between S-3APG and conventional antimyeloma agents. These cells showed the same sensitivity to S-3APG as MM.1S (IC₅₀ ~10 nM, data not shown). In contrast, thalidomide failed to inhibit any of the cell lines that we tested, except minimally at very high concentrations (100 μM; Fig. 2A–C).” *Id.* at 2301. Lentzsch 2002 further discloses that “[c]oculture of MM.1S or Hs Sultan with BMSCs did not alter the antiproliferative effect of S-3APG. Hs Sultan and MM.1S cell growth was still inhibited by S-3APG in a dose-dependent fashion, with IC₅₀ ~10 nM, whereas thalidomide did not have a significant inhibitory effect up to 100 μM.” *Id.*

Moreover, Lentzsch 2002 discloses that “[f]urther demonstration of the antiangiogenic activity of S-3APG was obtained by the demonstration that Hs Sultan tumors, treated with S-3APG, showed significantly lower microvessel density than did tumors of the control group.” *Id.* at 2303. Lentzsch 2002 explains that “[h]aving shown that 3-SAPG acted as a strong antiangiogenic agent, we were interested in determining whether S-3APG would still have an antitumor effect *in vivo* on tumor lines resistant to the antiproliferative activity of S-3APG *in vitro*. Thus, we compared the *in vivo* effects of S-3APG and thalidomide on *in vitro* resistant myeloma cells in immunodeficient mice. Treatment of RPMI-8226 tumors with S-3APG suppressed the growth of this *in vitro* resistant myeloma line as compared with control and thalidomide-treated mice. Tumors in S-3APG-treated animals were significantly smaller than in thalidomide-treated animals beginning day 11, whereas the inhibition of tumor growth by thalidomide was not statistically significant (Fig. 3E).” *Id.* at 2303-04.

Lentzsch 2002 concludes that they had “shown that S-3APG is a powerful antimyeloma ... agent that has antiproliferative and antiangiogenic effects without toxicity to cells of the bone marrow microenvironment and hematopoietic progenitor cells.” *Id.* at 2304.

Lentzsch 2002 qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having been received for publication on November 1, 2001, accepted for publication on March 4, 2002 and publishing on April 15, 2002.

48. Sorbera

Sorbera discloses the efficacy and safety of CC-5013 (i.e. lenalidomide) in phase II clinical studies involving 70 patients with refractory or relapsed multiple myeloma. Sorbera at 430. Sorbera further discloses that lenalidomide is dosed at 15 mg twice daily, or 30 mg once daily, for 3 weeks with 1 week of rest. *Id.*

Sorbera qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having published in May 2003.

49. Anderson

Anderson discloses a phase II trial of CC-5013 (i.e. lenalidomide) in patients with relapsed/refractory multiple myeloma. Anderson at 30. Anderson further discloses that lenalidomide was dosed at 15 mg twice daily, or 30 mg once daily, for 3 weeks with 1 week of rest. *Id.*

Anderson qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having published in October 2003.

50. Richardson IV

Richardson IV discloses a phase II trial of CC-5013 (i.e. lenalidomide) in patients with relapsed/refractory multiple myeloma. Richardson IV at 104a. Richardson IV further discloses that lenalidomide was dosed at 15 mg twice daily, or 30 mg once daily, for 3 weeks with 1 week of rest. *Id.*

Richardson IV qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having published on November 16, 2002.

51. The '291 patent

U.S. Patent No. 5,712,291 ("the '291 patent") is titled "Methods and Compositions for Inhibition of Angiogenesis." The Children's Medical Center Corporation ("CMCC") is listed as the assignee on the face of the '291 patent and Robert D'Amato is named as the sole inventor. The '291 patent discloses "[a] method of treating undesired angiogenesis in a human or animal comprising the step of administering to the human or animal with the undesired angiogenesis a composition comprising an effective amount of . . . 3-aminothalidomide." '291 patent at claim 1. 3-aminothalidomide is another name for pomalidomide. The '291 patent also discloses

administration of pomalidomide to treat undesired angiogenesis that “occurs in blood borne tumors” and “leukemia.” *See id.* at claims 65 and 77. The ’291 patent discloses that “angiogenesis has been associated with blood-born tumors such as leukemia, any of various acute or chronic neoplastic diseases of the bone marrow in which unrestrained proliferation of white blood cells occurs, usually accompanied by anemia, impaired blood clotting, and enlargement of the lymph nodes, liver, and spleen. It is believed that angiogenesis plays a role in the abnormalities in the bone marrow that give rise to leukemia-like tumors.” *Id.* at 3:23-30. Thus, the ’291 patent discloses that pomalidomide can be administered to “treat undesired angiogenesis” that “occurs in” blood-borne cancers. The ’291 patent discloses that “[f]or oral administration to humans, a dosage of between approximately 0.1 to 300 mg/kg/day, preferably between approximately 0.5 and 50 mg/kg/day, and most preferably between approximately 1 to 10 mg/kg/day, is generally sufficient.” *Id.* at 13:17-21.

On August 7, 2001, Entremed, Inc. announced that the ’291 patent claims ENMD-0995 “for treating angiogenic-mediated diseases, including cancer.” The ’291 patent qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(b), having issued on January 27, 1998, which is more than a year before the earliest possible priority date.

52. Robert

Robert discloses that the chemotherapy drug etoposide was administered for 21 consecutive days in a 28 day cycle. “A group of 17 patients received a 7-day infusion of etoposide (schedule A) every 21 days at doses from 30 to 75 mg/m² per day, and a second group of 37 patients a 21-day infusion (schedule B) every 28 days at doses from 18 to 40 mg/m² per day.” Robert at 459. Treatment cycles were repeated on day 21 or day 28 for schedule A and B, respectively. *Id.* at 460. Thus, Robert teaches that the chemotherapy drug is administered for 21 consecutive days followed by 7 consecutive days of rest in a 28 day cycle.

Robert qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1992, which is more than a year before the earliest possible priority date.

53. Samlowski

Samlowski discloses a phase II trial of the chemotherapy drug gemcitabine and further discloses that a total of 26 eligible patients were registered to receive a dose of gemcitabine weekly for 3 weeks, followed by a 1 week rest period. Samlowski at 311.

Samlowski qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a) or § 102(b), having published in 2001.

54. Lee

Lee discloses a trial of chemoradiation therapy with two drugs during the 21 days of drug administration, which consisted of two cycles of chemotherapy with oral etoposide on days 1-21 and intravenous cisplatin on days 1 and 8 of a 28-day cycle. Lee at 479, 484. Thus, Lee teaches that etoposide, a chemotherapy drug, could be administered for 21 consecutive days followed by 7 days of rest in a 28 day cycle.

Lee qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1998, which is more than a year before the earliest possible priority date.

55. Chemotherapy 1992

Chemotherapy 1992 discloses that the chemotherapeutic drug hexamethylmelamine could be administered for 21 consecutive days in a 28 day cycle. "Most treatment regimens employ [hexamethylmelamine] at a dose of 4 to 12 mg/kg body weight for 14 days to 21 days, with cycles repeated at 28- to 42-day intervals." Chemotherapy 1992 Edition at 401-402. Thus,

Chemotherapy 1992 teaches that the chemotherapeutic drug is administered for 21 consecutive days followed by 7 consecutive days of rest in a 28 day cycle.

Chemotherapy 1992 qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1992, which is more than a year before the earliest possible priority date.

56. Weber 1999

Weber 1999 discloses that patients with resistant myeloma who did not respond to initial treatment with thalidomide “were treated with a combination of their previously maximally tolerated dose of thalidomide and intermittent dexamethasone.” Weber 1999 at 604a. Weber 1999 reports that “[partial response] was achieved in 4 of 10 pts. (40%) with primary resistant disease and 5 of 16 pts. (31%) with resistant relapse for overall response rates of 50% for primary refractory disease and 41% for myeloma in refractory relapse.” *Id.* Weber 1999 further discloses dose titration of thalidomide to determine the maximally tolerated and effective dose of the drug for the treatment of multiple myeloma. *Id.* at 604a.

Weber 1999 qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1999, which is more than a year before the earliest possible priority date.

57. The '177 patent

The '177 patent discloses “compressible starches suitable for use as binders in tablets or capsules.” '177 patent at 1:6-7. The '177 patent further discloses “a compressible starch, useful as a . . . binder-diluent for capsules, which consists essentially of a free-flowing compressible starch powder.” *Id.* at 3:52-56. The '177 patent discloses “an admixture of the above compressible starch and an effective amount of a wet granulation binder, e.g., pregelatinized starch.” *Id.* at 4:4-7. The '177 patent suggests that the properties of the binder—compressible

and free-flowing—make it suitable for use in conventional dry dosage capsule-filling methods. *See id.* at 1:34-41.

The '177 patent qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having issued in 1985, which is more than a year before the earliest possible priority date.

58. Hus

Hus discloses that thalidomide is an effective drug, with an acceptable degree of toxicity, in patients with refractory multiple myeloma. Hus at 404. As rationale for treating refractory or relapsed myeloma patients with thalidomide, Hus reported on previous work which had shown that “thalidomide inhibits angiogenesis and causes apoptosis of newly created vessels. Thalidomide also shows immunomodulatory properties which regulate the secretion of many cytokines, such as interleukin (IL)-2, tumor necrosis factor (TNF) and IL-6.” *Id.* at 404. Among those treated, Hus observed “a clinical response . . . in 27 (51%): there was a major response in 7 patients, a partial response in 12 and a minor response in 8.” *Id.* Further, Hus reported that “[a]fter 12 months of treatment, 6 of our responder patients developed progressive disease: 3 of these patients were then successfully treated with VAD. It should be stressed that these patients were refractory to VAD before thalidomide treatment.” *Id.* at 407. Hus further disclosed treating multiple myeloma patients as young as 32 and as old as 79 with thalidomide monotherapy. Hus at 405.

Hus qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in April 2001, which is more than a year before the earliest possible priority date.

59. Oken

Oken discloses a Phase III comparison of accepted treatments for multiple myeloma, including melphalan and prednisone (MP), with vincristine, carmustine, melphalan, cyclophosphamide, and prednisone (VBMCP). *See* Oken at 1561. Oken further discloses a treatment regimen for multiple myeloma that comprises administering a combination of chemotherapeutics for a specific number of consecutive days within certain intervals. *Id.* at 1562. Accordingly, Oken's treatment regimen comprises an interval wherein the various chemotherapeutics are administered for a number of consecutive days, followed by a number of days of rest from administration of the chemotherapeutics until the next cycle of treatment.

Oken qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1997, which is more than a year before the earliest possible priority date.

60. Alkeran 2001 Label

Alkeran 2001 Label discloses that existing multiple myeloma treatments on the market as of the earliest possible priority date of the '262, '939 and '428 patents utilized a cyclical dosing regimen comprising an administration period followed by a rest period to allow for recovery. Alkeran is indicated for "the palliative treatment of multiple myeloma and for the palliation of non-resectable epithelial carcinoma of the ovary." Alkeran 2001 Label at Indications. The Dosage and Administration states that "[t]he usual oral dose is 6 mg (3 tablets) daily. The entire daily dose may be given at one time. The dose is adjusted, as required, on the basis of blood counts done at approximately weekly intervals. After 2 to 3 weeks of treatment, the drug should be discontinued for up to 4 weeks, during which time the blood count should be followed carefully." *Id.* at Dosage and Administration. Other dosing regimens comprising an administration period followed by a rest period are further described. *Id.*

Alkeran 2001 Label qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having published in November 2001.

61. Knight

In 2001, former vice presidential candidate Geraldine Ferraro attended a congressional hearing in an effort to persuade lawmakers to increase federal funding for blood cancer research. Knight reports that Ms. Ferraro told her story “how her own multiple myeloma is being successfully treated with the once-reviled drug thalidomide.” Knight at 1. Knight also reports a recent study where “nearly 80 percent of [multiple myeloma] patients responded to the combination of thalidomide and the steroid dexamethasone.” *Id.*

Knight mentions that the Senate hearing was attended by John Holaday, then the chief executive of EntreMed, and John Jackson, then the chairman and chief executive of Celgene. Knight at 1. Knight also mentions that EntreMed and Celgene are competitors, providing one example where “EntreMed collects royalties on Celgene’s thalidomide sales.” *Id.* at 2.

Knight reports that “[n]ew drugs derived from or based on thalidomide could become a billion-a-year or even bigger business if they prove effective against not only blood cancers but also solid tumors, which are much more common.” Knight also reports that “Celgene calls its new compounds IMiDs” that “have shown none of thalidomide’s long list of troubling side effects.” Knight quotes Celgene’s Jackson as saying that “I would imagine that in myeloma it would replace thalidomide.” Knight at 3-4.

Knight qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having published on June 25, 2001.

62. Szelényi

Szelényi discloses the results of a phase II study of a combination of chemotherapeutic agents for the treatment of multiple myeloma. Szelényi at 105. Szelényi states that “[t]he

treatment regimen consisted of cyclophosphamide 200 mg/m² p o or i v day 1-4, adriamycin 30 mg/m² i v on day 1 and dexamethasone 40 mg p o day 1-4 (CAD),” which “was repeated every three weeks.” *Id.* Szelényi reports that “[a]ll patients were evaluated for toxicity,” and that “[l]eukopenia or thrombocytopenia grade 3 or 4 was observed in 18% and 6% of all treatment cycles, respectively.” *Id.* at 106. Szelényi discloses, however, that “[s]evere thrombocytopenia did not compromise the treatment if treatment intervals were prolonged to four weeks.” *Id.* at 108.

Thus, Szelényi discloses a treatment regimen for multiple myeloma that comprises administering a combination of chemotherapeutics for a specific number of consecutive days within certain intervals. Accordingly, Szelényi’s treatment regimen comprises an interval wherein the various chemotherapeutics are administered for a number of consecutive days, followed by a number of days of rest from administration of the chemotherapeutics until the next cycle of treatment. Furthermore, Szelényi states that the observed toxicity of the chemotherapeutics can be mitigated without comprising efficacy by modifying the treatment interval, particularly by extending the treatment cycle from three to four weeks, i.e., 28 days.

Szelényi qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(b), having published in January 2001, which is more than a year before the earliest possible priority date.

63. Chu

Chu discloses, among other things, that “the treatment-free interval between cycles should be the shortest possible time necessary for recovery of the most sensitive normal target tissue, which is usually the bone marrow” because “long intervals between cycles negatively affect dose intensity.” Chu at 292

Chu qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having published in November 2001.

64. WO 02/059106

WO 02/059106 is titled "Isoindole-imide Compounds, Compositions, and Uses Thereof" and discloses isoindole-imide compounds such as pomalidomide and their use for treating cancer. For example, WO 02/059106 discloses pomalidomide in Formula I and Formula V wherein X and Y are C=O, R1 and R2 are H, and n = 0. WO 02/059106 at 6:13-7:13, 13:21-32. WO 02/059106 discloses that "[t]he compounds are particularly useful for treating cancers of the blood and bone marrow, such as multiple myeloma ..." *Id.* at 1:30-31, 21:15-16, 78:9-10, and 79:14-15. WO 02/059106 also discloses that "[p]referably, the compounds and compositions of the invention are administered orally" and "[i]n general, suitable dosage ranges for oral administration are about 0.001 milligrams to about 20 milligrams of a compound of the invention per kilogram body weight per day, preferably, about 0.7 milligrams to about 6 milligrams, more preferably, about 1.5 milligrams to about 4.5 milligrams. In a preferred embodiment, a mammal, preferably, a human is orally administered about 0.01 mg to about 1000 mg of a compound of the invention per day, more preferably, about 0.1 mg to about 300 mg per day, or about 1 mg to about 250 mg in single or divided doses." *Id.* at 80:18, 82:30-83:1. WO 02/059106 further discloses that "[p]referred unit oral-dosage forms include pills, tablets, and capsules, more preferably capsules. Typically such unit-dosage forms will contain about 0.01 mg, 0.1 mg, 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, 50 mg, 100 mg, 250 mg, or 500 mg of a compound of the invention, preferably, from about 5 mg to about 200 mg of compound per unit dosage." *Id.* at 83:5-9.

WO 02/059106 qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having published in August 2002.

65. WO 02/064083

WO 02/064083 is titled “Synthesis of 3-Amino-Thalidomide and its Enantiomers” and discloses new and useful analogs of 3-amino-thalidomide (i.e., pomalidomide). WO 02/064083 at Abstract, 14:4-8; 14:22-15:15. WO 02/064083 lists as assignee The Children’s Medical Center Corporation. WO 02/064083 teaches:

[I]t is clear that angiogenesis plays a major role in the metastasis of cancer. If this angiogenic activity could be repressed or eliminated, then the tumor, although present, would not grow. In the disease state, prevention of angiogenesis could avert the damage caused by the invasion of the new microvascular system. Therapies directed at control of the angiogenic processes could lead to the abrogation or mitigation of these diseases.

Angiogenesis has been associated with a number of different types of cancer, including solid tumors and blood-borne tumors. Angiogenesis is also associated with blood-borne tumors, such as leukemias, lymphomas, multiple myeloma, and any of various acute or chronic 15 neoplastic diseases of the bone marrow in which unrestrained proliferation of white blood cells occurs, usually accompanied by anemia, impaired blood clotting, and enlargement of the lymph nodes, liver and spleen. It is believed to that angiogenesis plays a role in the abnormalities in the bone marrow that give rise to leukemia and 20 lymphoma tumors and multiple myeloma diseases.

Id. at 9:1-20. WO 02/064083 also teaches that “studies of the S(-) and R(+) enantiomers of 3-aminothalidomide, particularly S(-)-3-amino-thalidomide, show that these compounds are as potent as inhibitors of angiogenesis. These studies indicate that these compounds are useful for the treatment of angiogenesis-associated diseases. As indicated above, one angiogenesis-associated group of diseases is cancer.” *Id.* at 23:23-24:2. Further, “[e]xamples of specific types of cancer which can be treated with the S(-)- and R(+) enantiomers of 3-amino-thalidomide include ... multiple myeloma.” *Id.* at 24:6-13. Moreover, “S(-)3-amino-thalidomide showed potent antiangiogenic and anti-tumor activity in various *in-vito* and *in-vivo* tumor models.” *Id.* at 15:8-10. WO 02/064083 discloses that “[f]or oral administration to humans, a dosage of between approximately 0.1 to 300 mg/kg/day, preferably between approximately 0.5 and 50

mg/kg/day, and most preferably between approximately 0.1 to 2 mg/kg/day, is generally sufficient.” *Id.* at 18:10-18. Claim 3 of WO 02/064083 discloses “[a] method of inhibiting angiogenesis in a human or animal comprising administering to the human or animal with undesired angiogenesis an angiogenesis inhibiting amount of 3-amino-thalidomide, wherein the stereoisomer consists essentially of S(-)-3-amino-thalidomide or R(+)-3-amino-thalidomide. *Id.* at 34:16-21. Claim 7 states, “[t]he method of Claim 3, wherein the effective amount is from about 0.1 and about 1 mg/kg/day.” *Id.* at 35:5-6. *See also id.* at claims 5-6. WO 02/064083 further discloses that pomalidomide was dosed at 50 to 200 mg/kg/day in mice. *Id.* at 32, Table 1. WO 02/064083 discloses that “an effective amount” “can be readily determined by an appropriately skilled person, taking into account the condition to be treated, the route of administration and other relevant factors. Such a person will readily be able to determine a suitable dose, mode and frequency of administration.” *Id.* at 33:7-12.

WO 02/064083 qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(a), having published on August 22, 2002, or § 102(e), based on its claim of priority to 60/250,219 filed November 30, 2000 and/or its filing date of November 30, 2001. WO 02/064083 has the same or substantially the same disclosure as U.S. Patent Nos. 8,153,806 and 7,812,169, which are also prior art to the ’262, ’939 and ’428 patents.

66. WO 02/43720 (“Hwu”)

WO 02/43720 (“Hwu”) is titled “Compositions and Methods for the Treatment of Cancer.” Hwu discloses compositions comprising pomalidomide for the treatment of cancer. For example, Hwu discloses that “[p]referred thalidomide derivatives are the amino analogues of thalidomide such as amino-thalidomide,” which includes pomalidomide. Hwu at 19:12-13. Hwu further discloses that the compositions can be administered in a capsule form including excipients. *Id.* at 32:7, 32:29-33:1-5. Suitable excipients include fillers such as mannitol and

pre-gelatinized starch. *Id.* at 36:7-10. Hwu further discloses that compositions containing a thalidomide derivative can administered in combination with dexamethasone. *Id.* at 22:10-16; 24:16.

Hwu qualifies as prior art to the '262, '939, '428 and '427 patents under at least 35 U.S.C. § 102(a), having published on June 6, 2002, or § 102(e), based on its claim of priority to 60/250,130 filed December 1, 2000 and/or its filing date of December 3, 2001.

67. Hideshima Abstract

Hideshima Abstract concludes that “Thal and the IMiDs therefore represent a new treatment paradigm targeting both the tumor cell and the microenvironment to overcome classical drug resistance and achieve improved outcome in MM.” Hideshima Abstract at 304a.

Hideshima qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 2000, which is more than a year before the earliest possible priority date.

68. FDA Guideline for Industry

FDA Guideline for Industry discloses guidance for performing studies in life-threatening diseases, such as cancer. FDA Guideline for Industry at 5-6. FDA Guideline for Industry teaches that “[p]arallel dose-response study designs with placebo, or placebo-controlled titration study designs (very effective designs, typically used in studies of angina, depression, hypertension, etc.) would not be acceptable in the study of some conditions, such as life-threatening infections or potentially curable tumors, at least if there were effective treatments known.” *Id.* at 5. Furthermore, “because in those therapeutic areas considerable toxicity could be accepted, relatively high doses of drugs are usually chosen to achieve the greatest possible beneficial effect rapidly.” *Id.* FDA Guideline for Industry further discloses that “the choice of study design and study population in dose-response trials will depend on the phase of

development, the therapeutic indication under investigation, and the severity of the disease in the patient population of interest. For example, the lack of appropriate salvage therapy for life-threatening or serious conditions with irreversible outcomes may ethically preclude conduct of studies at doses below the maximum tolerated dose.” *Id.* at 7.

FDA Guideline for Industry qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(b), having published in 1994, which is more than a year before the earliest possible priority date.

69. Storer

Storer discloses that phase I clinical trials are used to estimate the maximum tolerable dose (MTD) of a new cancer drug. Storer at 925. Storer further discloses that these trials are typically implemented *ad hoc* with a small patient population where the MTD is found during dose escalation. *Id.* “Escalation continues until the number of patients experiencing a given degree of toxicity meets some set criterion, at which point the stopping dose or the next lower dose is taken as the MTD.” *Id.*

Storer qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(b), having published in 1989, which is more than a year before the earliest possible priority date.

70. Adjei

Adjei discloses a phase I study using a potential anticancer agent. Adjei at 1871. Twenty patients with solid tumors received 92 courses of escalating doses given orally twice a day (b.i.d.) for 7 days out of every 3 weeks. *Id.* Based on observed gastrointestinal toxicity (nausea, vomiting, and diarrhea) the maximum tolerated dose (MTD) was found to be 350 mg b.i.d. for subsequent studies. *Id.*

Adjei qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 2000, which is more than a year before the earliest possible priority date.

71. Greco

Greco discloses the phase I study using oral etoposide. Greco at 305. Fifty-two patients with advanced cancer who were resistant to all standard therapy were administered oral etoposide for 21 consecutive days in varying dosage. *Id.* The MTD was determined to be 50 mg/m²/d with myelosuppression as the dose-limiting toxicity. *Id.*

Greco qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1991, which is more than a year before the earliest possible priority date.

72. Zangari 2001

Zangari 2001 discloses a phase I study of lenalidomide (i.e. CC5013) in multiple myeloma patients who had relapsed after high dose chemotherapy. Zangari 2001, Abstract #3226. Zangari 2001 further discloses that 5 to 50 mg of lenalidomide was administered to patients for 4 weeks. *Id.* The maximum dose allowed in this study was 50 mg/day. *Id.*

Zangari 2001 qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. §§ 102(a), and/or 102(b), having been presented publicly at the 43rd Annual Meeting of the American Society of Hematology on December 7-11, 2001.

73. Friedman

Friedman provides guidance in performing clinic trials of cancer drugs. Friedman teaches the use of Phase I studies, Phase II studies, Phase III trials, Phase IV trials, and combinations thereof to determine safe and efficacious doses of potential new drugs. Friedman at 3-5. Friedman states that:

Most phase I designs are relatively simple. One of the first steps in evaluating drugs is to estimate how large a dose can be given before unacceptable toxicity is experienced by patients. This dose is usually referred to as the maximally tolerated dose, or MTD. Much of the literature has discussed how to extrapolate animal model data to the starting dose in humans or how to step-up the dose levels to achieve the MTD. As Storer and DeMets describe, there is a sparsity of phase I design literature; somewhat surprising since the goals are not dissimilar from those of bioassay methods for which a large literature exists.

In estimating the MTD in cancer drug development, the investigator usually starts with a very low dose and escalates the dose until a prespecified level of toxicity in patients is obtained. Typically, a small number of patients, usually three, are entered sequentially at a particular dose. If no specified level of toxicity is observed, the next predefined higher dose level is used. If unacceptable toxicity is observed in any of the three patients, an additional number of patients, usually three, are treated at the same dose. If no further toxicity is seen, the dose is escalated to the next higher dose. If additional unacceptable toxicity is observed, then the dose escalation is terminated and that dose, or perhaps the previous dose, is declared to be the MTD. This particular design assumes that the MTD occurs when approximately one third of the patients experience unacceptable toxicity. Variations of this design exist, but most are similar.

Id. at 3-4.

Friedman qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1998, which is more than a year before the earliest possible priority date.

74. Fuse

Fuse discloses that “Phase 1 studies are conducted to characterize the toxic effects of drugs and to determine the maximal tolerated dose (MTD). One-tenth of the dose lethal to 10% of the mice (LD₁₀) is often used as a starting dose and the dose is gradually increased by modified Fibonacci steps. The same strategy is often used regardless of the mechanism responsible for the cytotoxicity to tumor cells. The MTD must be administered to achieve the maximum therapeutic effects of most anti-cancer drugs used in clinical therapy.” Fuse at 133-134. Fuse discusses methods for predicting the human MTD based on pharmacokinetic and pharmacodynamics consideration. *See generally* Fuse.

Fuse qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1995, which is more than a year before the earliest possible priority date.

75. Collins

Collins generally discloses using *in vivo* models and pharmacology studies to develop phase I trials, and provides examples of typically phase I procedures for anticancer drugs. For example, Collins discloses that “since clinical pharmacokinetic measurements are already part of many phase I trials, human data could be directly compared with mouse data if mouse pharmacology studies were completed before clinical trials were initiated. Once the starting dose in a phase I clinical trial has been evaluated, subsequent doses are escalated until the maximum tolerated dose is reached. The rate of escalation is empirically defined by a modified Fibonacci series. This universal escalation scheme is applied to all drugs, with no modifications based upon pharmacology or other factors.” Collins at 73. Collins qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1986, which is more than a year before the earliest possible priority date.

76. Barlogie 2001

Barlogie 2001 discloses that thalidomide had shown “significant activity in refractory multiple myeloma,” based on a follow up Phase II trial. Barlogie 2001 at 250. Barlogie 2001 teaches that “available clinical trial information involving at least 20 patients confirms that thalidomide is active in one third of patients in single agent trials for refractory disease, with response rates increasing to 50% to 60% in combination with dexamethasone and to as high as 80% in combination with dexamethasone and chemotherapy.” *Id.* Barlogie 2001 further discloses that “[s]even single agent [thalidomide] trials in refractory disease showed an overall response rate (PPR \geq 50%) of 36% among 352 patients with available information. The addition

of dexamethasone increases the response rate beyond 50%.” *Id.* at 256-57. Barlogie 2001 notes that “[n]ewer, more potent, and less toxic derivatives of thalidomide are being evaluated.” *Id.* at 250.

Barlogie 2001 qualifies as prior art under 35 U.S.C. § 102(b), as it published in July 2001, over a year prior to the earliest possible priority date.

77. Dredge/Marriott

Dredge/Marriott discloses that pomalidomide (i.e. CC-4408 (ACTIMID™)) “has recently been found to possess an acceptable safety profile in a phase I trial for relapsed/refractory multiple myeloma,” and that it “has an acceptable toxicity profile with antitumor activity and should be evaluated in future phase II studies in hematological and solid tumor malignancies.” Dredge/Marriott at 433-34.

Dredge/Marriott published in 2002 and qualifies as prior art under 35 U.S.C. § 102(a) or 102(b).

78. Smith II

Smith II discloses that phase I trials “are designed to estimate the MTD, with the usually unstated assumption that this dose would have the greatest chance of therapeutic efficacy with acceptable toxicity. Efficacy of the agent given at MTD would be evaluated in a subsequent phase II trial.” Smith II at 288.

Smith II qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(b), having published in 1996, which is more than a year before the earliest possible priority date.

79. EORTC

EORTC discloses that “[a]t the start of a phase I study patients are deliberately treated at what is predicted to be a non-toxic and often non-therapeutic dose. This is usually 1/10th of the

dose lethal to 10% of mice so treated (the LD₁₀), with the drug given by the same schedule and the dose expressed in units of mass/surface area (e.g. mg/m²). Provided toxicity is not observed at the starting dose, doses are then escalated until side-effects are encountered which are deemed to be dose-limiting. A dose is then selected which is considered safe for phase II trials.” EORTC at 1083.

EORTC qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1987, which is more than a year before the earliest possible priority date.

80. Rubinstein

Rubinstein discloses that “[t]he objective of a phase I trial is to determine the appropriate dosage of an agent or combination to be taken into further study and to provide initial pharmacologic and pharmacokinetic studies. It is generally assumed, at this stage of testing, that increased dose is associated with increased chance of clinical efficacy. Therefore, the phase I trial is designed as a dose-escalation study to determine the maximum tolerable dosage (MTD), that is, the maximum dose associated with an acceptable level of dose-limiting toxicity (DLT-- usually defined to be grade 3 or above toxicity, excepting grade 3 neutropenia unaccompanied by either fever or infection). This MTD is then taken into further testing.” Rubinstein at 1. Rubinstein further discloses standard phase I designs to determine MTD. *See generally*, Rubinstein.

Rubinstein qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having published in 2003.

81. Singhal II

Singhal II discloses that “[t]halidomide inhibits the production of tumor necrosis factor (TNF- α), interleukin 6 (IL-6), IL-10, and IL-12. Thalidomide enhances the production of IL-2,

interferon, IL-4, and IL-5. It increases the total lymphocyte and the CD4+ and CD8+ T-cell numbers and costimulates T-lymphocytes. Thalidomide also augments natural killer cell cytotoxicity in myeloma and inhibits angiogenesis. Recently, it has also been found to inhibit nuclear factor- κ B (NF- κ B). Thalidomide analogs and bortezomib share the above described properties of thalidomide to varying degrees. They induce the apoptosis of myeloma cells, inhibit the upregulation of IL-6, overcome IL-6-mediated protection against dexamethasone-induced apoptosis of myeloma cells, and inhibit TNF- α -induced NF- κ B production.” Singhal II at 227. Singhal II further discloses that CC-5013 (i.e. lenalidomide) is being investigated for treating myeloma, or has strong preclinical evidence of antimyeloma activity. *Id.* at 226. Singhal II teaches that “[o]ur long-term experience (2 years) with CC-5013 in a single patient treated on a compassionate-use protocol revealed consistent myelosuppression at a daily dose of 15 mg. Initially, the disease responded to 5 mg, then to 10 mg when progression occurred on 5 mg, and then to 15 mg when progression occurred on 10 mg. The combination of 10 mg CC-5013 and alternate-day prednisone therapy worked well for a period when 15 mg could not be tolerated.” *Id.* at 229.

Singhal II qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having published in April 2003.

82. Barlogie 2003

Barlogie 2003 discloses that “based on the increased potency and reduced toxicity profile of CC-5013 (i.e. lenalidomide) compared with thalidomide, a study of CC-5013 in patients with relapsed/refractory disease following transplantation was initiated. Patients are randomized to CC-5013 25 mg daily for 20 days versus CC-5013 50 mg every other day for 10 days. Preliminary results indicate the superiority of the 25-mg arm, with 40% of patients randomized

to that arm experiencing a paraprotein reduction of 50% or greater. These preliminary results corroborate the role for thalidomide and CC-5013 in relapsed/refractory and newly diagnosed multiple myeloma based on the UAMS phase II study as well as several other studies of these agents outside of UAMS.” Barlogie 2003 at 33.

Barlogie 2003 qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(a), having published in October 2003.

83. Richardson 2006

Richardson 2006 discloses a phase 2 study of lenalidomide for patients with relapsed or relapsed and refractory multiple myeloma. Richardson 2006 further discloses that “patients were randomized to receive either 30 mg once-daily or 15 mg twice-daily oral lenalidomide for 21 days of every 28-day cycle. Patients with progressive or stable disease after 2 cycles received dexamethasone.” Richardson 2006 at 3458.

Richardson 2006 qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(a), having published in July 2006.

84. Alexanian

Alexanian discloses the successful treatment of multiple myeloma patients with the combination of thalidomide and dexamethasone after intensive previous treatment for multiple myeloma. Alexanian at 1116-1117. Alexanian qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(a), having been received for publication in November 2001, accepted for publication in February 2002, and published on July 7, 2002.

85. Kyle

Kyle discloses treatment with thalidomide and dexamethasone in patients with active, previously untreated multiple myeloma. Kyle at 583. “Thalidomide was administered in an initial dosage of 200 mg/d for 2 weeks and then increased as tolerated (in 200-mg increments at 2-week

intervals) to a maximum daily dose of 800 mg. Dexamethasone was given orally in a dosage of 40 mg/d on days 1 through 4, 9 through 12, and 17 through 20 in odd cycles and 40 mg/d on days 1 through 4 in even cycles at monthly intervals.” *Id.* Kyle further discloses that “[t]he addition of dexamethasone to thalidomide may produce a response in patients who are refractory to thalidomide” and “[d]examethasone plus thalidomide produces an objective response in approximately three fourths of previously untreated MM patients.” *Id.* at 587. Kyle also discloses that “[p]atients with relapsed myeloma were treated with thalidomide dosed at 200 mg/d, with 200-mg escalations every 2 weeks to a maximum daily dose of 800 mg. Prior chemotherapy had failed and five (16%) patients had experienced relapse following stem cell transplantation. Ten (38%) of the 26 patients who had received at least two cycles of therapy obtained a response” *Id.* at 583.

Kyle qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(a), having published in December 2001.

86. Zangari 2002

Zangari 2002 discloses that “thalidomide has proven activity in refractory multiple myeloma (MM)...” Zangari 2002 at 1168. Zangari 2002 qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(a), having published in August 2002.

87. Jönsson

Jönsson discloses the thalidomide derivative pomalidomide at Table 1, compound 7. Jönsson at 524. Jönsson further discloses that pomalidomide was known to be less teratogenic than thalidomide. *See Id.* at 523-24. Jönsson qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(b), having published in 1972, which is more than a year before the earliest possible priority date.

88. Adler

Adler reports that, as of December 1994, clinical trials of thalidomide for patients with certain cancers had been planned, including advanced Kaposi's sarcoma and melanoma, among others. Adler at 424. Adler also reports that Andrulis Pharmaceuticals Corp., one of the few U.S. manufacturers of thalidomide at that time, was involved in a number of thalidomide clinical trials. *Id.* at 425. Adler further reports that Celgene was developing drugs that "mimic thalidomide." *Id.*

Adler qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1994, which is more than a year before the earliest possible priority date.

89. Bor

Bor discloses the historical developments associated with thalidomide. *See generally*, Bor. Bor qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1995, which is more than a year before the earliest possible priority date.

90. Lipkin

Lipkin discloses the historical developments associated with thalidomide and its derivatives. *See generally*, Lipkin. Lipkin teaches that "[i]n designing these new molecules, Muller and Stirling said, they improved the potency of the portion of thalidomide exhibiting medicinal properties and removed the segment causing birth defects." *Id.* at 171.

Lipkin qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1995, which is more than a year before the earliest possible priority date.

91. Tsenova 2002

Tsenova 2002 cites to Davies (reference 9) and discloses that IMiD3 is indicated to be α -3-aminophthalimido-glutarimide (i.e. pomalidomide). Tsenova 2002 at 1889. However, Tsenova 2002 incorrectly identified IMiD3 as α -3-aminophthalimido-glutarimide (i.e., pomalidomide), which was corrected by way of an erratum which identifies IMiD3 as [3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione]” (i.e., lenalidomide). See Tsenova Erratum.

Tsenova 2002 qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having published in June 2002.

92. Stirling II

Stirling II discloses that thalomid was initially marketed as a sedative and that clinical trials of thalidomide for patients with certain cancers had been planned. “The National Cancer Institute has several studies ongoing or planned to test the usefulness of thalidomide in various cancers conditions, e.g., cancer of the prostate and breast, and Kaposi’s sarcoma.” Stirling II at 312.

Stirling II qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1992, which is more than a year before the earliest possible priority date.

93. Richardson V

Richardson V discloses that “the IMiDs appear to have significantly greater potency than thalidomide, with a potentially more favorable toxicity profile. On this basis, phase I studies of CC-5013, also known as IMiD 3, are now under way in patients with refractory or relapsed multiple myeloma, and preliminary results are encouraging.” Richardson V at 645-646. Richardson V further discloses:

Although thalidomide was initially used to treat multiple myeloma because of its antiangiogenic effects, the mechanism of its antimyeloma activity appears to be more complex (Figure 2). Preclinical studies of thalidomide and its potent analogs (also known as immunomodulatory drugs, IMiDs) suggest that these drugs act against myeloma in several ways. First, there appears to be a direct effect on the myeloma cell and/or bone marrow stromal cell, which inhibits tumor growth and survival. Second, adhesion of myeloma cells to bone marrow stromal cells (BMSCs) triggers secretion of cytokines, which augment myeloma cell growth and survival (59-61) and confer drug resistance (62); importantly, thalidomide modulates adhesive interactions (14) and thereby may alter tumor cell growth, survival, and drug resistance. Third, cytokines secreted into the bone marrow microenvironment by myeloma cells and/or BMSCs, such as IL-6, IL-1,8, IL-10, and *TNF- α* may augment myeloma cell growth and survival (61, 63), and thalidomide may alter their secretion and bioactivity (64). Fourth, thalidomide decreases the secretion of VEGF, IL-6 (65), and BFGF by myeloma and/or BMSCs.

Id. at 635-636.

Richardson V qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having published in 2002.

94. Vogelsang

Vogelsang discloses that a group from Johns Hopkins University led by Georgia Vogelsang reported that thalidomide was useful for the treatment of chronic graft-versus-host disease ("GVHD"). *See generally*, Vogelsang.

Vogelsang qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1997, which is more than a year before the earliest possible priority date.

95. Sampaio 1991

Sampaio 1991 discloses that thalidomide selectively inhibits TNF- α . Sampaio 1991 at 699. Sampaio 1991 qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1991, which is more than a year before the earliest possible priority date.

96. Sampaio 1992

Sampaio 1992 discloses that thalidomide inhibits TNF- α . Sampaio 1992 at 1729. Sampaio 1992 qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1992, which is more than a year before the earliest possible priority date.

97. D'Amato 1994

D'Amato 1994 discloses that thalidomide is a potent angiogenesis inhibitor *in vivo* and that “the ability of thalidomide to inhibit angiogenesis induced by pharmacologic doses of bFGF supports the hypothesis that thalidomide directly inhibits an essential component of angiogenesis and does not operate through effects on TNF- α production.” D'Amato 1994 at 4085.

D'Amato 1994 qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1994, which is more than a year before the earliest possible priority date.

98. Olson

Olson discloses a study in which “[t]wenty-one patients with fourteen types of tumor [including multiple myeloma] were treated with thalidomide for 1 to 34 weeks (total dose 4.2 to 354.0 Gm.) without objective evidence of tumor regression.” Olson 296. Olson concludes “that further trials of this drug in tumors not sensitive to other agents, especially tumors of mesenchymal origin, and its use in conjunction with x-ray therapy, is warranted.” Olson at 297.

Olsen qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1994, which is more than a year before the earliest possible priority date.

99. Rajkumar 2000

Rajkumar 2000 discloses that “[r]ecent evidence suggests that angiogenesis is increased in multiple myeloma and has prognostic value in the disease. Based on the increased angiogenesis observed in myeloma, thalidomide (Thalomid) has been studied as antiangiogenic therapy. Although its mechanism of action in myeloma is unclear, several trials show that thalidomide is active in 25% to 35% of patients with relapsed myeloma. Since many patients who respond have failed other active regimens, including transplantation, these results are impressive.” Rajkumar 2000 at 11.

Rajkumar 2000 qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(b), having published in 2000, which is more than a year before the earliest possible priority date.

100. He Abstract

He Abstract discloses that Vogelsang’s group considered six thalidomide derivatives, including 3-amino-thalidomide (i.e. pomalidomide), in an effort to find a thalidomide derivative having improved pharmacological properties. *See generally*, He Abstract. The name, 3-aminothalidomide (aka, 3-azathalidomide), is based on the numbering of the phthalimide ring. *Id.*

He Abstract qualifies as prior art to the ’262, ’939 and ’428 patents under at least 35 U.S.C. § 102(b), having published in 1993, which is more than a year before the earliest possible priority date.

101. Schey Report

Schey Report discloses that Celgene announced “that its ... immunomodulatory drug Actimid (i.e. CC-4047, [pomalidomide]) demonstrated anti-tumor activity in multiple myeloma and exhibited an acceptable toxicity profile, according to an interim analysis of an ongoing, 18-

patient phase I/II trial testing the drug. Celgene reported the results at the International Society for Experimental Hematology meeting in Montreal. The company previously had tested Actimid only in healthy volunteers.” Schey Report at 1. Schey Report further discloses that in the dose-escalating phase I/II trial, pomalidomide was administered to 18 relapsed or refractory multiple myeloma patients. *Id.* at 1.

Schey Report qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(a), having published in July 2002.

102. EntreMed Press Release (Aug. 7, 2001)

EntreMed Press Release (Aug. 7, 2001) discloses that EntreMed selected ENMD 0995 (*i.e.*, 3-amino-thalidomide or pomalidomide) for further development with respect to the treatment of myeloma. EntreMed announced that it had reached a supply agreement with respect to ENMD 0995 (*i.e.*, pomalidomide) to support preclinical studies because of its favorable profile as a potent anti-angiogenic and anti-tumor properties.

EntreMed Press Release (Aug. 7, 2001) qualifies as prior art to the '262, '939 and '428 patents under at least U.S.C. § 102(a), having published in August 2001.

103. Moreira

Moreira discloses that thalidomide enhances TNF- α mRNA degradation. Moreira at 1675. Moreira qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1993, which is more than a year before the earliest possible priority date.

104. Muller 1997

Muller 1997 discloses that enantiomeric forms of thalidomide and EM12 had been isolated and determined to undergo extensive racemization in vitro and in vivo. Muller 1997 at 22. Muller 1997 qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C.

§ 102(b), having published in 1997, which is more than a year before the earliest possible priority date.

105. Heger

Heger discloses a study that enantiomeric forms of thalidomide and EM12 had been isolated and determined to undergo extensive racemization in vitro and in vivo. Heger at 117. Heger qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1994, which is more than a year before the earliest possible priority date.

106. Smith I

Smith I discloses the chemical structure of pomalidomide (i.e. 4-amino-thalidomide). The name 4-amino-thalidomide is based on the numbering of the isoindoline ring. Smith I at 202.

Smith I qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1965, which is more than a year before the earliest possible priority date.

107. Edwards

Edwards discloses the historical developments associated with thalidomide. *See generally*, Edwards. Edwards qualifies as prior art to the '262, '939 and '428 patents under at least 35 U.S.C. § 102(b), having published in 1987, which is more than a year before the earliest possible priority date.

108. The '791 publication

The '791 publication is titled "Methods for treating cutaneous lupus using aminoisoindoline compounds." The '791 publication teaches pharmaceutical compositions and methods of treating, preventing and/or managing cutaneous lupus by the administration of compounds such as 4-(amino)-2-(2,6-dioxo(3 -piperidyl))-isoindoline-1,3-dione (pomalidomide). '791 publication at ¶¶ [0002]-[0003].

The '791 publication teaches that the pharmaceutical compositions may be oral dosage forms, including oral capsules. *Id.* at ¶ [0119]. Tablets and capsules are the most advantageous oral dosage forms due to their ease of administration. *Id.* at [0120]. Suitable excipients for oral dosage forms include starches, diluents and lubricants. *Id.* at [0120]-[0122].

The '791 publication also teaches that lactose-free oral dosage forms may contain fillers, such as pregelatinized starch or mannitol and that oral dosage forms may contain various lubricants, including magnesium stearate and silica gel. *Id.* at ¶¶ [0112], [0124], [0127]. The '791 publication teaches a range of 0.1 mg to 5 mg pomalidomide per day and, specifically, that the daily dose of pomalidomide may be 0.1, 1, 2, 5, 10 or 25 mg per day. *Id.* at ¶ [0096], claim 29.

The '791 publication qualifies as prior art to the '427 patent under at least 35 U.S.C. § 102(b), having published in July 2007, which is more than a year before the earliest possible priority date.

109. The '733 patent

The '733 patent, entitled “Formulations for pharmaceutical agents ionizable as free acids or free bases,” lists Narmada Shenoy, Waranush Shorasuchart, and Arun Koparkar as its inventors. It is assigned on the face of the patent to Sugan, Inc. The '733 patent teaches pharmaceutical compounds that may be formulated, *inter alia*, as oral dosage forms. '733 patent at 150:17. Oral formulations may comprise, e.g., one or more pharmaceutically acceptable fillers, diluents and lubricants. *Id.* at 150:31-39. Suitable diluents include pre-gelatinized starch and mannitol, as well as combinations of diluents. *Id.* at 150:49-51. Suitable lubricants include magnesium stearate and sodium stearyl fumarate. *Id.* at 150:66 – 151:3.

The oral dosage forms may also include flow enhancers, such as colloidal silicon dioxide. *Id.* at 151:3-6. Pharmaceutical formulations can be prepared in push-fit capsules. *Id.* at 157:45-

52. Capsules may contain active ingredient in admixture with filler, binder and/or lubricant. *Id.* at 157:48-51.

Lactose-free capsules were prepared, which included pregelatinized starch, mannitol, croscarmellose sodium and magnesium stearate. *Id.* at Example 6 and Table 9, 252:10-61. The '733 Patent teaches that granulations can be encapsulated in, e.g. size 0, 1, 2, 3 or 4 capsules. *Id.* at 252:64-67.

The '733 patent qualifies as prior art to the '427 patent under at least 35 U.S.C. §§ 102(a) and 102(b), having issued in April 2005, which is more than a year before the earliest possible priority date.

II. BASIS OF DEFENDANTS' CONTENTION THAT THE ASSERTED CLAIMS OF THE ZELDIS PATENTS ARE INVALID

Pursuant to L. Pat. R. 3.3 and 3.6(c), Defendants provide Plaintiff with the following written bases for its invalidity contentions with respect to the asserted claims of the '262, '939 and '428 patents, referred to collectively as the Zeldis Patents.

A. Priority Date

1. '262 Patent Priority Date

The '262 patent, entitled "Methods For Treating Multiple Myeloma Using 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione," issued on June 12, 2012 from Application No. 12/229,074 ("the '074 application"), filed August 19, 2008. Defendants contend August 19, 2008 is the earliest effective filing date of the asserted claims. According to the '262 patent, the '074 application purports to be a division of application No. 10/438,213, filed on May 15, 2003, now Patent No. 7,968,569, which purports to claim the benefit of U.S. Provisional Patent Application No. 60/380,842, filed on May 17, 2002, and also U.S. Provisional Patent Application

No. 60/424,600, filed on Nov. 6, 2002. The earliest possible priority date for the aforementioned patent is May 17, 2002, which is the date one of the provisional applications was filed.

However, Defendants dispute that any of the claims of the '262 patent are entitled to priority to U.S. Patent Appl. No. 10/438,213; U.S. Provisional Patent Application No. 60/380,842; and/or U.S. Provisional Patent Application No. 60/424,600. None of these earlier filed applications disclose the claimed invention in the manner required by 35 U.S.C. § 112(a). This contention is further supported in Sections II. E and II. F. For example, neither U.S. Patent Appl. No. 10/438,213; nor U.S. Provisional Patent Application No. 60/380,842; nor U.S. Provisional Patent Application No. 60/424,600 provide sufficient written description and/or enablement support for the asserted claims of the '262 patent. For example, there is insufficient written description support in any of these earlier filed applications for the '262 patent's claim elements "treating multiple myeloma;" "from about 1mg to about 5mg per day of the compound having the formula" depicted; "a pharmaceutically acceptable salt, solvate or stereoisomer thereof for 21 consecutive days followed by seven consecutive days of rest from administration of said compound;" "40 mg of dexamethasone;" "wherein the compound is administered in an amount of about 4 mg per day;" "wherein the compound is administered in an amount of about 3 mg per day;" "wherein the compound is administered in an amount of about 2 mg per day;" "wherein the compound is administered in an amount of about 1 mg per day;" "wherein the dexamethasone is orally administered in an amount of 40 mg once daily on days 1, 8, 15 and 22 of each 28 day cycle;" "wherein the dexamethasone is orally administered in an amount of about 40 mg once a week of each 28 day cycle;" "wherein the compound is administered in a capsule;" "wherein the compound is administered orally in a capsule of 1 mg, 2 mg, 3 mg, or 4 mg;" "wherein the capsule comprises the compound, mannitol and pre-gelatinized starch." Thus,

Defendants contend that disclosures prior to the filing of the '262 patent on August 19, 2008 are prior art to the '262 patent under at least 35 U.S.C. §§ 102(a), (b), (e), (f) and/or (g); that disclosures prior to the filing of U.S. Provisional Patent Application No. 60/424,600 on Nov 6, 2002 are prior art to the '262 patent under at least 35 U.S.C. §§ 102(a), (b), (e) (f), or (g); and that disclosures prior to the filing of U.S. Provisional Patent Application No. 60/380,842 on May 17, 2002 are prior art to the '262 patent under at least 35 U.S.C. §§ 102(a), (b), (e), (f) or (g).

Defendants further contend that the named inventor on the face of the '262 patent is Jerome B. Zeldis did not himself invent the claimed subject matter, and that he cannot establish an earlier day of invention for the claimed subject matter.

2. '939 Patent Priority Date

The '939 patent, entitled "Methods for treating multiple myeloma with 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione" issued on March 18, 2014 from Application No. 13/782,728 ("the '728 application"), filed March 1, 2013. Defendants contend March 1, 2013 is the earliest effective filing date of the asserted claims. According to the '939 patent, the '728 application purports to be a continuation of U.S. patent application Ser. No. 13/488,888, filed June 5, 2012, which purports to be a continuation of U.S. patent application Ser. No. 12/640,702, filed Dec. 17, 2009, now U.S. Pat. No. 8,198,306, which purports to be a continuation application of U.S. patent application Ser. No. 10/438,213, filed May 15, 2003, now U.S. Pat. No. 7,968,569, which purports to claim the benefit of U.S. provisional application Nos. 60/380,842, filed May 17, 2002, and 60/424,600, filed Nov. 6, 2002. The earliest possible priority date for the '939 patent is May 17, 2002, which is the date one of the provisional applications was filed.

However, Defendants dispute that any of the claims of the '939 patent are entitled to priority to U.S. Patent Appl. No. 13/782,728; U.S. Provisional Patent Application No.

60/380,842 and/or U.S. Provisional Patent Application No. 60/424,600. None of these earlier filed applications disclose the claimed invention in the manner required by 35 U.S.C. § 112(a). This contention is further supported in Sections II. E and II. F. For example, neither U.S. Patent Appl. No. 13/782,728; nor U.S. Provisional Patent Application No. 60/380,842; nor U.S. Provisional Patent Application No. 60/424,600 provide sufficient written description and/or enablement support for the asserted claims of the '939 patent. For example, there is insufficient written description support in any of these earlier filed applications for the '939 patent's claim elements "treating multiple myeloma;" "from about 1mg to about 5mg per day of the compound having the formula" depicted; "a pharmaceutically acceptable salt, solvate or stereoisomer thereof wherein the compound is administered in one or more cycles, each of which comprises administering the compound for a period of time followed by a period of rest;" "40 mg of dexamethasone;" "wherein the compound is administered in an amount of about 4 mg per day;" "wherein the compound is administered in an amount of about 3 mg per day;" "wherein the compound is administered in an amount of about 2 mg per day;" "wherein the compound is administered in an amount of about 1 mg per day;" "wherein the dexamethasone is orally administered in an amount of 40 mg once daily on days 1, 8, 15 and 22 of each 28 day cycle;" "wherein the dexamethasone is orally administered in an amount of about 40 mg once a week of each 28 day cycle;" "wherein the compound is administered in a capsule;" "wherein the compound is administered orally in a capsule of 1 mg, 2 mg, 3 mg, or 4 mg;" "wherein the capsule comprises the compound, mannitol and pre-gelatinized starch."

Thus, Defendants contend that disclosures prior to the filing of the '939 patent on March 1, 2013 are prior art to the '939 patent under at least 35 U.S.C. §§ 102(a), (b), (e), (f) and/or (g); that disclosures prior to the filing of U.S. Provisional Patent Application No. 60/424,600 on Nov

6, 2002 are prior art to the '262 patent under at least 35 U.S.C. §§ 102(a), (b), (e) (f), or (g); and that disclosures prior to the filing of U.S. Provisional Patent Application No. 60/380,842 on May 17, 2002 are prior art to the '262 patent under at least 35 U.S.C. §§ 102(a), (b), (e), (f) or (g).

Defendants further contend that the named inventor on the face of the '939 patent is Jerome B. Zeldis did not himself invent the claimed subject matter, and that he cannot establish an earlier day of invention for the claimed subject matter.

3. '428 Patent Priority Date

The '428 patent, entitled "Methods for treating multiple myeloma with 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione" issued on May 27, 2014 from Application No. 13/782,612 ("the '612 application"), filed March 1, 2013. Defendants contend March 1, 2013 is the earliest effective filing date of the asserted claims. According to the '428 patent, the '612 application purports to be a continuation of U.S. patent application Ser. No. 13/488,888, filed June 5, 2012, which purports to be a continuation of U.S. patent application Ser. No. 12/640,702, filed Dec. 17, 2009, now U.S. Pat. No. 8,198,306, which purports to be a continuation application of U.S. patent application Ser. No. 10/438,213, filed May 15, 2003, now U.S. Pat. No. 7,968,569, which purports to claim the benefit of U.S. provisional application Nos. 60/380,842, filed May 17, 2002, and 60/424,600, filed Nov. 6, 2002. The earliest possible priority date for the '428 patent is May 17, 2002, which is the date one of the provisional applications was filed.

However, Defendants dispute that any of the claims of the '428 patent are entitled to priority to U.S. patent application Ser. No. 13/488,888; U.S. patent application Ser. No. 12/640,702; U.S. patent application Ser. No. 10/438,213; U.S. Provisional Patent Application No. 60/380,842 and/or U.S. Provisional Patent Application No. 60/424,600. None of these earlier filed applications disclose the claimed invention in the manner required by 35 U.S.C. §

112(a). This contention is further supported in Sections II. E and II. F. For example, neither U.S. patent application Ser. No. 13/488,888; U.S. patent application Ser. No. 12/640,702; U.S. patent application Ser. No. 10/438,213; nor U.S. Provisional Patent Application No. 60/380,842; nor U.S. Provisional Patent Application No. 60/424,600 provide sufficient written description and/or enablement support for the asserted claims of the '428 patent. For example, there is insufficient written description support in any of these earlier filed applications for the '428 patent's claim elements "treating multiple myeloma;" "from about 1mg to about 5mg per day of the compound having the formula" depicted;" "a pharmaceutically acceptable salt, solvate or stereoisomer thereof for 21 consecutive days followed by seven consecutive days of rest in a 28 day cycle;" "40 mg of dexamethasone;" "wherein the compound is administered in an amount of about 4 mg per day;" "wherein the compound is administered in an amount of about 3 mg per day;" "wherein the compound is administered in an amount of about 2 mg per day;" "wherein the compound is administered in an amount of about 1 mg per day;" "wherein the dexamethasone is orally administered in an amount of 40 mg once daily on days 1, 8, 15 and 22 of each 28 day cycle;" "wherein the dexamethasone is orally administered in an amount of about 40 mg once a week of each 28 day cycle;" "wherein the compound is administered in a capsule;" "wherein the compound is administered orally in a capsule of 1 mg, 2 mg, 3 mg, or 4 mg;" "wherein the capsule comprises the compound, mannitol and pre-gelatinized starch."

Thus, Defendants contend that disclosures prior to the filing of the '428 patent on March 1, 2013 are prior art to the '428 patent under at least 35 U.S.C. §§ 102(a), (b), (e), (f) and/or (g); that disclosures prior to the filing of U.S. Provisional Patent Application No. 60/424,600 on Nov 6, 2002 are prior art to the '262 patent under at least 35 U.S.C. §§ 102(a), (b), (e) (f), or (g); and

that disclosures prior to the filing of U.S. Provisional Patent Application No. 60/380,842 on May 17, 2002 are prior art to the '262 patent under at least 35 U.S.C. §§ 102(a), (b), (e), (f) or (g).

Defendants further contend that the named inventor on the face of the '428 patent is Jerome B. Zeldis did not himself invent the claimed subject matter, and that he cannot establish an earlier day of invention for the claimed subject matter.

B. Prior Art That Anticipates or Renders Obvious Each Asserted Claim

Each and every asserted claim of the Zeldis patents are invalid as anticipated or rendered obvious by the prior art. The relevant prior art that would have been available to a person of ordinary skill in the art includes at least the following references, which are prior art to the Zeldis Patents under at least 35 U.S.C. §§ 102(a), (b), (e), (f) and/or (g):

1. Muller, G., et al., *Amino-Substituted Thalidomide Analogs: Potent Inhibitors of TNF- α Production*, Biorg. Med. Chem. Lett., 9:1625-1630 (1999) ("Muller"); [DEFS_POM_00011054-059]
2. U.S. Patent No. 5,635,517 ("the '517 patent"); [DEFS_POM_00000175-185]
3. U.S. Patent No. 5,731,325 ("the '325 patent (Andrulis)"); [DEFS_POM_00000149-156]
4. U.S. Patent No. 6,316,471 ("the '471 patent"); [DEFS_POM_00000157-174]
5. Rajkumar, et al., Abstract #722, Thalidomide plus dexamethasone (Thal/Dex) and thalidomide alone (thal) as first line therapy for newly diagnosed myeloma (MM), Blood, 96(11):168a (2000) ("Rajkumar"); [DEFS_POM_00011159-160]
6. Durie, B.G.M., and Stepan, D.E., *Efficacy of low dose thalidomide in multiple myeloma*, Electronic Journal of Oncology, 1:1-8 (2000) ("Durie"); [DEFS_POM_00003826-3833]
7. Palumbo, A., et al., Low-dose thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma, Haematologica, 86:399-403 (2001) ("Palumbo"); [DEFS_POM_00011142-146]
8. Singhal, S., et al., *Antitumor activity of thalidomide in refractory multiple myeloma*, N. Engl. J. Med., 341:1565-1571 (1999) ("Singhal"); [DEFS_POM_00011432-438]

9. Hideshima, T., et al., Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy, *Blood*, 96(9):2943-50 (2000) ("Hideshima 2000"); [DEFS_POM_00013305-312]
10. Corral, L.G., et al., Differential Cytokine Modulation and T Cell Activation by Two Distinct Classes of Thalidomide Analogs That Are Potent Inhibitors of TNF- α , *J. of Immunology*, 163:380-386 (1999) ("Corral I"); [DEFS_POM_00013259-266]
11. Corral, L.G., et al., *Immunomodulation by thalidomide and thalidomide analogues*, *Ann. Rheum. Dis.*, 58 (Suppl. I): I107- I113 (1999) ("Corral II"); [DEFS_POM_00002190-196]
12. Weber, et al., Abstract #719, *Thalidomide with dexamethasone for resistant multiple myeloma*, *Blood*, 96(11):167a (2000) ("Weber 2000"); [DEFS_POM_00012320-322]
13. Rajkumar, S.V., and Kyle, R.A., *Thalidomide in the treatment of plasma cell malignancies*, *J. of Clinical Oncology*, 19(16):3593- 3595 (2001) ("Rajkumar & Kyle"); [DEFS_POM_00013404-406]
14. Kropff, et al., Abstract #725, *Hyperfractionated cyclophosphamide in combination with pulsed dexamethasone and thalidomide (hyper- CDT) in primary refractory or relapsed multiple myeloma*, *Blood*, 96(11):168a (2000) ("Kropff"); [DEFS_POM_00011003-004]
15. Klausner, et al., *The Effect of Thalidomide on the Pathogenesis of Human Immunodeficiency Virus Type I and M. tuberculosis Infection*, *J. of Acquired Immune Deficiency Syndromes and Human Retrovirology*, 11:247-257 (1996) ("Klausner I"); [DEFS_POM_00010983-997]
16. Klausner, et al., *Short analytical review: thalidomide as an anti-TNF- α inhibitor: implications for clinical use*, *Clinical Immunology and Immunopathology*, 81(3):219-223 (1996) ("Klausner II"); [DEFS_POM_00010998-1002]
17. Market Letter (June 18, 2001), *Celgene drug promises activity in solid tumors*, (Market Publications Ltd.) ("June Market Letter"); [DEFS_POM_00013346-348]
18. Market Letter (October 15, 2001), *Celgene's Revlimid an orphan drug, says FDA*, (Market Publications Ltd.) ("October Market Letter"); [DEFS_POM_00013394-396]
19. Hideshima, T., et al., *The Proteasome Inhibitor PS-341 Inhibits Growth, Induces Apoptosis, and Overcomes Drug Resistance in Human Multiple Myeloma Cell*, *Cancer Research*, 61:3071–3076 (2001) ("Hideshima 2001"); [DEFS_POM_00013313-318]
20. PCT Publication WO 98/03502 ("WO 98/03502"); [DEFS_POM_00012323-370]

21. Marriott, et al., *Immunotherapeutic and antitumour potential of thalidomide analogues*, Expert Opinion on Biological Therapy, 1(4):675-682 (2001) (“Marriott 2001”); [DEFS_POM_00013372-380]
22. D’Amato, et al., *Mechanism of Action of Thalidomide and 3-Aminothalidomide in Multiple Myeloma*, Seminars in Oncology, 28(6):597-601 (2001) (“D’Amato 2001”); [DEFS_POM_00002201-205]
23. Aviles, et al., *Dexamethasone, all trans retinoic acid and interferon alpha 2a in patients with refractory multiple myeloma*, Cancer Biotherapy & Radiopharmaceuticals, 14(1):23-26 (1999) (“Aviles”); [DEFS_POM_00001749-753]
24. Thalomid Product; [DEFS_POM_00000018-22; DEFS_POM_00000023-44; DEFS_POM_00000051-74; DEFS_POM_00000075-94; DEFS_POM_00000126-129; DEFS_POM_00012565-93]
25. Dimopoulos, et al., *Thalidomide and dexamethasone combination for refractory multiple myeloma*, Ann Oncology, 12:991- 995 (2001) (“Dimopoulos”); [DEFS_POM_00002206-210]
26. 42nd annual meeting of the American Society of Hematology, Abstract # 3617, Abstracts # 2485-87 (2000) (“2000 Abstracts”); [DEFS_POM_00000045-047]
27. Davies, et al., *Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma*, Blood, 98:210-216 (July 2001) (“Davies”); [DEFS_POM_00013267-274]
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Defendants reserve the right to rely on any combination of the above prior art in an obviousness defense, including to illustrate the background knowledge of a person of ordinary skill in the art, to demonstrate the motivation to combine prior art references, to demonstrate reasonable expectation of success,² and to rebut any evidence of validity raised by Plaintiff. Brief summaries of the disclosures of some of the prior art references listed are set forth above under Section I. B.

The following combinations of prior art references are exemplary of the many combinations of prior art references that render the asserted claims of the '262 patent obvious:

1. Any one or more of Marriott 2002, Schey I, Schey II and Schey III.
2. Any one or more of '517 patent, WO 98/03502, '291 patent, '471 patent, WO 02/064083.
3. Any one or more of Muller, Corral I, Corral II, Celgene Annual Report 1999, Celgene Press Releases, Hideshima 2000, Lentzsch 2003, Mitsiades, Marriott 2001, 2000 Abstracts, Fujita, Richardson III, Knight, Hideshima Abstract and any one or more of the references in combination 2 and/or combination 1.
4. Any one or more of Davies, Gupta, Dredge 2001, Dredge 2003, D'Amato 2001, Hideshima 2000, Lentzsch 2002, and the references in combination 3.
5. Hideshima 2000, D'Amato 2001, Davies, Gupta, Dredge 2001, Celgene Annual Report 1999, Celgene Press Releases, Lentzsch 2002, WO 02/43720, Lentzsch 2001, and the references in combination 4.
6. Any one or more of the references in combination 5 with any one or more of Thalomid[®], the '325 patent, Durie, Celgene Press Releases, Celgene Annual Report 1999, Palumbo, Rajkumar, Dimopoulos, Singhal, Klausner

² The Local Patent Rules do not require Defendants to identify references solely used for background, motivation to combine, and/or reasonable expectation of success. *See* L.Pat.R. 3.3, 3.6; *Sanofi-Aventis U.S. LLC v. Fresenius Kabi USA, LLC*, No. 14-7869 (MAS), ECF No. 148, Ltr. Order; *id.* at Jan. 20, 2017 Case Management Conference Tr. 9:19-11:2. Thus, Defendants reserve the right to rely on additional references not disclosed herein for background, motivation to combine, and/or reasonable expectation of success.

I, Klausner II, Rajkumar & Kyle, Weber II, Hus, Knight, Edwards, Adler, Bor, Lipkin.

7. Any one or more of the references in combination 5 with any one or more of Stirling, Dredge 2002, Raje, Richardson II, Sorbera, Anderson, Richardson IV, Richardson 2006, Celgene Press Releases, June Market Letter, October Market Letter, Marriott 2002, Richardson I.
8. Any one or more of the references in combination 5 with any one or more of '325 patent, Klausner I, Klausner II, Chemotherapy 1992, Robert, Samlowski, Lee, Alkeran 2001 Label, Szelenyi, Oken.
9. Any of the previous combinations with any one or more of Weber 2000, Weber 1999, Durie, Palumbo, Hideshima 2000, Rajkumar & Kyle, Dimopoulos, Mitsiades, Richardson 2001, Richardson 2002, Rajkumar, Aviles, Kropff; 2000 Abstracts, Lentzsch 2003, Richardson II, Richardson III, Schey II, Knight.
10. Any one or more of Muller, the '517 patent, the '325 patent, Durie, Palumbo, Singhal, Hideshima 2000, Corral II, Weber, Rajkumar, Rajkumar & Kyle, Aviles, Kropff, Klausner I, October Market Letter, June Market Letter, Hideshima 2001.
11. Any one or more of Corral I, Corral II, Muller, the '517 patent, the '325 patent, Durie, Palumbo, Hideshima 2000, Rajkumar & Kyle, October Market Letter.
12. Any one or more of Weber 1999, D'Amato 2001, '291 patent, '517 patent, '177 patent, Palumbo, Szelenyi, Corral II, Corral I, Hideshima 2000, Davies, or Jönsson.
13. Any one or more of Singhal, '291 patent, Szelenyi, D'Amato 2001, Hus, '517 patent, '177 patent, Oken, Hideshima 2001, Weber 1999, Palumbo.
14. Any one or more of D'Amato 2001, Weber 1999, '291 patent, Singhal, Szelenyi, Hideshima 2001, Hus, '517 patent, '177 patent, and Palumbo.
15. Any one or more of Schey I, Schey II, Corral I, Corral II, Chemotherapy 1992 Edition, Robert, Palumbo, Dimopolous, Alexanian, Lentzsch 2002.
16. Any one or more of Alexanian, Samlowski, Lee, Robert, Corral I, Corral II, Dimopolous, Hideshima 2000, Kyle, Lentzsch 2002, Mitsiades, Muller, Palumbo, Richardson II, Richardson III, Richardson V, Robert, Schey I, Schey II, Sorbera, Zangari 2002, Chemotherapy 1992 Edition, Thalomid Product, WO 02/064083.

17. Any one or more of D'Amato 2001, the '471 patent, Lentzsch 2002, Hideshima 2000, the '517 patent.
18. Any one or more of Barlogie 2001, D'Amato 2001, Dredge/Marriott, Schey I.

This list is exemplary and does not constitute an exhaustive list of all possible combinations. Defendants also identify and incorporate the combinations identified below and in the claim charts attached as Exhibits A-C.

C. Invalidity Based on Anticipation/Obviousness Under 35 U.S.C. §102/§103

All Asserted Claims of the Zeldis Patents are invalid as anticipated and obvious in view of the prior art. All dependents claims are anticipated or obvious over the prior art for the reasons discussed with respect to the independent and other dependent claims from which they dependent and such arguments are incorporated by reference.

1. Method Of Treating Multiple Myeloma Comprising Administering To A Patient Having Multiple Myeloma

All claims of the Zeldis Patents recite a method of treating multiple myeloma comprising administering pomalidomide to a patient having multiple myeloma. At the outset, Defendants submit that at least the following portion of the preambles of the asserted claims of the Zeldis Patents, “[a] method of treating multiple myeloma,” is merely a statement of purpose or intended use, and is non-limiting, as the bodies of the asserted claims define structurally complete methods. Nevertheless, treating multiple myeloma with pomalidomide is anticipated and rendered obvious by of the prior art.

Pomalidomide,³ a structural analog of thalidomide, has been known in the art since at least 1972. Jönsson at 524 (compound 7 of Table 1). *See also, e.g.*, Smith I at 202; He Abstract.

³ Pomalidomide is also referred to as CC4047, CDC394, ENMD-0995 and Actimid. The ENMD-0995 manufacturing code was used by EntreMed Inc. (“EntreMed”). *See, e.g.*, EntreMed Press Release (August 7, 2001). Pomalidomide is also repeatedly referred to in

It was also known in the prior art that pomalidomide was effective in the treatment of oncogenic or cancerous conditions, and multiple myeloma is a form of cancer. *See, e.g.*, '471 patent at claim 16. *See also, e.g.*, '517 patent at 3:59-4:40; WO 98/03502 at 7:22-26, 5:20-29. More specifically, administration of pomalidomide to treat undesired angiogenesis that “occurs in blood borne tumors” was also known. *See* '291 patent at claims 65 and 77. Treatment of multiple myeloma with pomalidomide was also known. *See* WO 02/064083. Thus, based on these teachings, the person having ordinary skill in the art would have understood that pomalidomide was used in the treatment of multiple myeloma.

It was further known in the art that pomalidomide had anti-MM activity and was being investigated for its efficacy in the treatment of patients with multiple myeloma. *E.g.*, Davies; Hideshima 2000; Gupta; Dredge 2001; Dredge/Marriott; Dredge 2003; D'Amato 2001; Lentzsch 2001; Lentzsch 2002; WO 02/064083. *See also* FDA, Orphan Drug Designations and Approvals (FDA granted orphan drug status to S(-)-3-[3-amino-phthalimido]-glutaramide on March 14, 2002 for treatment of multiple myeloma); EntreMed Press Release (Nov. 7, 2002); EntreMed Press Release (Aug. 7, 2001). Additionally, pomalidomide was also known to have significantly higher potency than thalidomide and less toxicity. *See, e.g.*, EntreMed Press Release (August 7, 2001); EntreMed Press Release (April 15, 2002); EntreMed Press Release (Nov. 7, 2002); EntreMed Press Release (Dec. 10, 2002); Knight; PR Newswire, “EntreMed Commences ENMD 0995 Clinical Trial For Myeloma,” Nov. 13, 2002; Mitsiades; Marriott 2001; 2000 Abstracts; Fujita; Richardson III; Hideshima Abstract; Schey I; Schey Report.

D'Amato explains that “one analog of thalidomide, 3-aminothalidomide [pomalidomide], exhibited an unusual capacity to directly inhibit myeloma cell proliferation ... Thus 3-

publications as IMiD1; however, in some publications it is referred to as IMiD3. Pomalidomide is also referred to as 3-aminothalidomide (“3A-thalidomide”).

aminothalidomide was found to inhibit multiple myeloma through effects on both the tumor and vascular component.” D’Amato 2001 at Abstract. D’Amato explains that their studies showed a “remarkable property of 3-aminothalidomide,” in that “although thalidomide does not have any direct effect on myeloma cells in vitro, 3-aminothalidomide very potently inhibits myeloma cell growth.” D’Amato 2001 at 599. D’Amato provides that pomalidomide “has been reported to downregulate IL6. Since IL-6 is an important autocrine and paracrine growth factor for myeloma, this suggests the possibility that 3-aminothalidomide may directly inhibit myeloma cells through a suppression of IL-6.” *Id.* at 600. D’Amato concluded that “[r]ecent studies with thalidomide analogs have identified a molecule known as 3-aminothalidomide, which has the additional in vitro ability to directly suppress the proliferation of myeloma cells. This analog offers great promise for the treatment of multiple myeloma through its combined antiangiogenic and antiproliferative activities.” *Id.* at 600.

For example, Lentzsch 2002 identifies pomalidomide [S-3APG], which exhibited dual activity against B-cell neoplasias, and was able to “directly inhibit the proliferation of myeloma ... *in vitro* without showing toxicity to normal bone marrow stromal cells or hematopoietic progenitor cells.” Lentzsch 2002 at Abstract. Lentzsch teaches that “[i]n vivo, S-3APG treatment of drug resistant myeloma cell tumors in mice was able to produce complete and sustained regressions without any observed toxicity” and “inhibited angiogenesis more potently than thalidomide.” *Id.* Lentzsch also states that “[t]he initial characterization of S-3APG for activity included proliferation assays ... In these assays, we observed that S-3APG directly inhibits cultured myeloma and lymphoma cell lines. Lentzsch 2002 at 2301. Lentzsch explains that “[h]aving shown that 3-SAPG acted as a strong antiangiogenic agent, we were interested in determining whether S-3APG would still have an antitumor effect *in vivo* on tumor lines resistant

to the antiproliferative activity of S-3APG *in vitro*. Thus, we compared the *in vivo* effects of S-3APG and thalidomide on *in vitro* resistant myeloma cells in immunodeficient mice. Treatment of RPMI-8226 tumors with S-3APG suppressed the growth of this *in vitro* resistant myeloma line as compared with control and thalidomide-treated mice.” Lentzsch 2002 at 2303. Lentzsch concludes that they had “shown that S-3APG is a powerful antimyeloma ... agent that has antiproliferative and antiangiogenic effects without toxicity to cells of the bone marrow microenvironment and hematopoietic progenitor cells.” Lentzsch 2002 at 2304.

Additionally, Muller and Corral I reported on the activity of pomalidomide, referred to as compound 5a or CI-A, respectively. Muller at 1626; Corral I at 381, Table 1. Muller reported the structure-activity relationships of amino substitution of the phthaloyl ring of thalidomide, which resulted in compound 5a. Muller at 1626. Corral I and Muller both disclose that compound CI-A/5a, i.e., pomalidomide, is a more potent inhibitor of TNF- α —a key cytokine in the inflammatory cascade—than thalidomide. Muller at 1627 and 1629; Corral I at Table 1. In particular, compound CI-A/5a had a TNF- α IC₅₀ of 10 to 13 nM, which was significantly smaller than the IC₅₀ of approximately 200 μ M for thalidomide in a TNF- α inhibition study. Muller at 1628-9; Corral I at 380, Table 1. Muller reports that compound 5a “was found to be ~50,000 times more potent than thalidomide at inhibiting TNF- α levels in LPS stimulated human PBMC.” Muller at 1629. *See also* Marriott 2001 at 677, Table 2. Such results indicate a greater potency for pomalidomide over thalidomide.

Corral I also discloses that pomalidomide (referred to as compound CI-A) “induced significant increases in IL-12 production” in a T cell-dependent system. Corral I at 383. As can be seen in Figure 4, pomalidomide induced similar or greater levels of IL-12 production in the T-cell dependent system as thalidomide at far lower concentrations than thalidomide. *Id.* at 384.

Corral I determined the effect of thalidomide and certain IMiDs on IL-6 production in LPS-stimulated peripheral blood mononuclear cells, and states that “class I compounds significantly inhibited IL-6 levels.” *Id.* at 381. As can be seen in Figure 1, pomalidomide (compound CI-A) was the second most potent IMiD in inhibiting IL-6 levels, and had essentially the same activity as the most potent within the margin of error. *Id.* at 382. Corral I also discloses that IMiDs “were found to be efficient T cell costimulators leading to the augmented production of the T cell cytokines IL-2 and IFN- γ .” Corral I at 383. As can be seen in Figure 3, Corral I found that pomalidomide (compound CI-A) was a more potent stimulator of IL-2 and IFN- γ secretion than thalidomide. *Id.*

Corral II discloses studies on the anti-tumor effects of IMiDs, including lenalidomide and pomalidomide. Corral II at I109 Fig.1. Corral II further disclosed that “the more potent of these thalidomide analogues were found to be up to 50,000-fold more potent than thalidomide at inhibiting TNF α production.” Corral II at I109 Fig. 1. Corral II discloses that “IL12 has [] been shown to exhibit potent anti-tumour activity in murine tumour models through various mechanisms including the stimulation of natural killer cell activity, activation of CD8⁺ cytotoxic T cells and increased IFN γ mediated anti-angiogenesis.” Corral II at I111. Corral II states that “our recent findings that thalidomide and IMiDs preferentially costimulate CD8⁺ T cells and induce T cell dependent IL12 production suggest possible application[] of these drugs in . . . boosting anti-tumour immunity.” *Id.*

Hideshima 2000 determined whether thalidomide and IMiDs act directly on multiple myeloma cells by measuring 3H-TdR uptake in the presence of the drugs at various concentrations. Hideshima 2000 at 2945. Hideshima states that “all 3 IMiDs tested achieved 50% inhibition of DNA synthesis at concentrations (0.1-1.0 μ mol/L) corresponding to serum

levels that are readily achievable, both confirming their direct action on tumor cells and suggesting their potential clinical utility.” *Id.* at 2949. Hideshima also tested the effect of thalidomide and IMiDs on DNA synthesis in patient multiple myeloma cells, and reported that “[a]s was true for MM.1S and Hs Sultan MM cell lines, 3H-TdR uptake of patients’ MM cells was also inhibited by IMiDs (0.1-100 $\mu\text{mol/L}$) in a dose-dependent fashion, whereas the inhibitory effect of Thal, even at 100 $\mu\text{mol/L}$, was not significant.” *Id.* at 2946. Hideshima also “showed that IL-6 can overcome the effect of Thal and the IMiDs on MM cell lines and patient cells, suggesting that these novel drugs may, at least in part, be inhibiting IL-6 production.” *Id.* at 2949. Hideshima further stated that the study “suggest[s] that the IMiDs do not work only by directly inhibiting MAPK growth signaling and further support their potential activity in down-regulating IL-6 production.” *Id.*

Davies found that thalidomide and IMiDs “induced NK-cell-mediated lysis of MM cell lines and patient cells.” Davies at 216. Davies also measured cytokine levels of patients treated with thalidomide and found “that the decrease in paraprotein and the increase in NK cells was accompanied by an increase in IL-2 and IFN- γ secretion.” *Id.* Accordingly, Davies correlates the increased levels of secreted IL-2 and IFN- γ induced by thalidomide and NK-cell-mediated lysis of MM cell. Specifically, Davies states that “the direct effect of Thal on T cells results in an increase in IL-2 and IFN- γ secretion, which augments NK cell number and function.” *Id.*

It was also known that pomalidomide was well-tolerated in humans and under Phase I/II clinical study for multiple myeloma. *See e.g.*, Dredge/Marriott; Dredge 2003; Marriott 2002; Celgene Press Releases; Celgene Annual Report 1999; Schey I; Schey II; Schey III; Schey Report. For example, Schey I discloses a Phase I study using pomalidomide (i.e. CC4047) for the treatment of multiple myeloma. *See* Schey I. Schey II discusses the use of thalidomide and

thalidomide analogues in the treatment of multiple myeloma. Specifically, Schey II reports that analogues, including pomalidomide, have been developed to “improve efficacy and reduce toxicity,” and that two in particular, including pomalidomide, are in clinical development with promising results. *See* Schey II at 295. Schey II describes the clinical studies of pomalidomide in patients with relapsed or refractory myeloma and reports that the results are “very encouraging.” *Id.* at 296. *See also* Celgene Press Release (July 8, 2002); Celgene Press Release (Nov. 13, 2001); EntreMed Press Release (Aug. 7, 2001); PR Newswire, “EntreMed Commences ENMD 0995 Clinical Trial For Myeloma,” Nov. 13, 2002.

Thus, based on these teachings, the person having ordinary skill in the art would have understood that pomalidomide was effective in the treatment of multiple myeloma. They further would have understood that pomalidomide was a highly potent and promising therapy for the treatment of multiple myeloma because in addition to its antiangiogenic properties, pomalidomide was understood to directly and potently inhibit myeloma cell growth. Further, pomalidomide was known to induce increased IL-12 production in a T cell-dependent system more potently than thalidomide, inhibit IL-6 production in LPS-stimulated peripheral blood mononuclear cells at comparable levels as thalidomide, and stimulate production of IL-2 and IFN- γ from T cells more potently than thalidomide. It would have been expected that pomalidomide would be effective for treating patients with multiple myeloma, and it would have been obvious to use pomalidomide in that manner. The person having ordinary skill in the art would have reasonably expected success at least because the prior art suggests that thalidomide’s efficacy against multiple myeloma is due, at least in part, to modulation of these cytokine levels. *See, e.g.,* Corral II, Corral I, Hideshima, and Davies.

Moreover, the person of ordinary skill in the art would have been motivated to substitute pomalidomide for thalidomide, or for lenalidomide,⁴ and use it for treating multiple myeloma. The prior art showed that pomalidomide was a derivative of thalidomide with similar mechanisms of action and greater potency than thalidomide. *See, e.g.*, Celgene Annual Report 1999, Celgene Press Releases, Hideshima 2000, Lentzsch 2003, Mitsiades, Marriott 2001, 2000 Abstracts, Fujita, Richardson III, Knight, Hideshima Abstract, June Market Letter, October Market Letter. Likewise, the prior art taught that a similar IMiD, lenalidomide, with similar mechanisms of action and greater potency than thalidomide had been well-tolerated in humans and effective as a treatment for refractory and/or relapsing multiple myeloma. *Id.*

For example, the prior art disclosed that Revlimid® (lenalidomide) “ha[d] been granted orphan drug designation by the US Food and Drug Administration as a treatment for multiple myeloma.” October Market Letter at 1. October Market Letter reveals that Phase I/II clinical trials have “preliminary indications that up to 60% of patients enjoy a clinical response to” lenalidomide. *Id.* *See also* June Market Letter. The prior art further disclosed that lenalidomide was safe, well tolerated in humans during phase I/II studies, exhibited anti-MM activity, and was more potent and less toxic than thalidomide. *See e.g.*, Stirling at 602, Dredge 2002 at 1172; Celgene Press Release (February 29, 2000); Celgene Press Release (May 8, 2001); Raje, Sorbera, Anderson, Richardson IV, Richardson 2006, Celgene Press Release (June 7, 2001); June Market Letter, October Market Letter, Marriott 2002, Richardson I at 775a; Richardson II at 3063; Singhal II at 226, 229; Barlogie 2003 at 33; Richardson 2006; Richardson V at 645-646. Moreover, lenalidomide was shown to have anti-tumor effects in relapsed/refractory multiple

⁴ Lenalidomide is also referred to as CC5013, CDC501, ENMD-0997, Revimid and Revlimid. The ENMD-0997 manufacturing code was used by EntreMed. Lenalidomide is also typically referred to in publications as IMiD3; however, in some publications it is referred to as IMiD1.

myeloma, and anti-MM activity in lenalidomide was enhanced by dexamethasone. *See e.g.*, Richardson I at 775a; Richardson II at 3067; Celgene Press Release (May 8, 2001); Celgene Press Release (June 7, 2001); Barlogie 2003 at 33; Richardson 2006; Richardson V at 646. Pomalidomide and lenalidomide are IMiDs which are similar in structure, and also structurally similar to thalidomide. *See e.g.*, Richardson III at 116; Corral II at I109, Fig. 1; Celgene Press Release (September 3, 1998). Celgene identified pomalidomide and lenalidomide (i.e. CC-4047 and CC-5013, respectively) as two lead IMiDs. Celgene Annual Report 1999 at 4, 12-13.

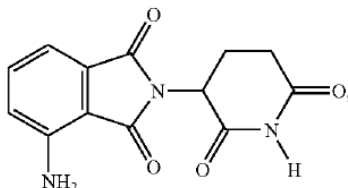
The prior art also disclosed use of thalidomide—the parent compound of pomalidomide—to treat multiple myeloma, against relapsed and refractory multiple myeloma, synergistic with dexamethasone. *See, e.g.*, Thalomid®; the '325 patent; Durie; Celgene Press Releases; Celgene Annual Report 1999; Palumbo; Rajkumar; Dimopoulos; Singhal; Rajkumar & Kyle; Weber II; Hus; Knight; Edwards; Adler; Bor; Lipkin; Olson; Rajkumar 2000; Kyle; Barlogie 2001; D'Amato 1994. For example, D'Amato 1994 discloses that thalidomide is a potent angiogenesis inhibitor in vivo and that “the ability of thalidomide to inhibit angiogenesis induced by pharmacologic doses of bFGF supports the hypothesis that thalidomide directly inhibits an essential component of angiogenesis and does not operate through effects on TNF- α production.” D'Amato 1994 at 4085. By 2001, “thalidomide [was]...considered as part of standard therapy for relapsed myeloma.” Rajkumar & Kyle at 3593. In clinical studies with thalidomide for treating subjects with refractory multiple myeloma, Singhal et al. showed a response rate of 32% in patients with relapsed, refractory myeloma. Singhal at 1565. The 32% response rate was impressive in that the rate was obtained on a patient population where “90% of the patients in this study had failed autologous stem-cell transplantation.” Rajkumar & Kyle at 3593. Other studies confirmed response rates of 25%-45% in patients with relapsed myeloma

taking thalidomide. *Id.* Barlogie 2001 disclosed that response rates in patients with refractory multiple myeloma increased to 50% to 60% when thalidomide was administered in combination with dexamethasone. Barlogie 2001 at 250.

The person having ordinary skill in the art would have been further motivated to administer pomalidomide instead of thalidomide because pomalidomide was known to be less teratogenic than thalidomide. *See* Jönsson at 523-24; Lipkin at 171. For example, Knight reported that “the IMiDs have shown none of thalidomide’s long list of troubling side effects.” Knight at 3. Celgene also reported that the IMiDs would replace thalidomide in myeloma since they are 100 to 1,000 times more potent than thalidomide. Knight at 3-4; *see also* Muller at 1629; Hideshima 2000 at 2945; D’Amato 2001 at 599-600; Lipkin at 171.

2. Administering Pomalidomide in the Recited Doses

Claim 1 of the ’262 patent recites administering “from about 1 mg to about 5 mg per day of a compound having the formula:



or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.” ’262 patent at 38:19-32. Claim 20 of the ’262 patent recites administering “from about 1 mg to about 5 mg per day of a compound” having the above formula. 39:11-25. Claims 10-13 and 21-24 of the ’262 patent further recite particular dosing amounts of pomalidomide, including 1, 2, 3, and 4 mg.

Claim 1 of the ’939 patent recites administering “from about 1 mg to about 5 mg per day of a compound” having the above formula “or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.” ’939 patent at 39:1-14. Claim 26 of the ’939 patent recites administering

“from about 1 mg to about 5 mg per day of a compound” having the above formula “or a solvate thereof.” 40:19-31. Claims 8-11 and 28 of the ’939 patent further recite particular dosing amounts of pomalidomide, including 1, 2, 3, and 4 mg.

Claim 1 of the ’428 patent recites administering “from about 1 mg to about 5 mg per day of a compound” having the above formula “or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.” ’428 at patent 39:5-18. Claim 26 of the ’428 patent recites administering “from about 1 mg to about 5 mg per day of a compound” having the above formula or a solvate thereof.” 40:22-34. Claims 8-11 and 24 of the ’428 patent further recite particular dosing amounts of pomalidomide, including 1, 2, 3, and 4 mg.

These features are anticipated and rendered obvious by the prior art. Effective amounts of pomalidomide were taught in multiple prior art references. Furthermore, determination of an effective amount of a drug is routine optimization for a person of ordinary skill in the art.

For example, WO 02/059106 discloses pomalidomide in Formula I and Formula V wherein X and Y are C=O, R1 and R2 are H, and n = 0. WO 02/059106 at 6:13-7:13, 13:21-32. WO 02/059106 discloses that “[t]he compounds are particularly useful for treating cancers of the blood and bone marrow, such as multiple myeloma ...” *Id* at 1:30-31, 21:15-16, 78:9-10, 79:14-15. WO 02/059106 also discloses that “[p]referably, the compounds and compositions of the invention are administered orally,” and “[i]n general, suitable dosage ranges for oral administration are about 0.001 milligrams to about 20 milligrams of a compound of the invention per kilogram body weight per day, preferably, about 0.7 milligrams to about 6 milligrams, more preferably, about 1.5 milligrams to about 4.5 milligrams. In a preferred embodiment, a mammal, preferably, a human is orally administered about 0.01 mg to about 1000 mg of a compound of the invention per day, more preferably, about 0.1 mg to about 300 mg per day, or about 1 mg to

about 250 mg in single or divided doses.” *Id.* at 80:18, 82:30-83:1. WO 02/059106 further discloses that “[p]referred unit oral-dosage forms include pills, tablets, and capsules, more preferably capsules. Typically such unit-dosage forms will contain about 0.01 mg, 0.1 mg, 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, 50 mg, 100 mg, 250 mg, or 500 mg of a compound of the invention, preferably, from about 5 mg to about 200 mg of compound per unit dosage.” *Id.* at 83:5-9.

Additionally, the ’471 patent teaches that pomalidomide could be administered orally to reduce TNF- α in the form of a capsule or tablet containing from 1 to 100 mg of drug per unit dosage. ’471 patent at 5:25-30, 8:26-28 and 28:64-67. WO 98/03502 taught that pomalidomide could be used for “[d]ecreasing THF α levels and/or increasing cAMP levels thus constitut[ing] a valuable therapeutic strategy for the treatment of many inflammatory, infectious, immunological, and malignant diseases. These include but are not restricted to ... oncogenic or cancerous conditions.” WO 98/03502 at 7:23-24, 5:20-26. WO 98/03502 further disclosed an oral dosage of 1 to 100 mg of pomalidomide per unit dosage. WO 98/03502 at 11:19-20. The ’517 patent teaches that “[o]ral dosage forms include tablets, capsules ... containing from 1 to 100 mg of drug per unit dosage.” ’517 patent at 5:62-64. Additionally, the ’291 patent disclosed that “[f]or oral administration [of pomalidomide] to humans, a dosage of between approximately 0.1 to 300 mg/kg/day, preferably between approximately 0.5 and 50 mg/kg/day, and most preferably between approximately 1 to 10 mg/kg/day, is generally sufficient.” ’291 Patent at 13:17-21. *See also, e.g.*, WO 02/064083 at 18:10-18. WO 02/064083 also specifically discloses from about 0.1 and about 2 mg/kg/day of 3-amino-thalidomide. WO 02/064083 at Claims 3, 7.

Thus, the prior art disclosed the dosing range of pomalidomide to be, e.g., 1 to 100 mg/day, 1 to 10 mg/day, or 0.1 to about 2 mg/day. “Where there is a range disclosed in the prior art, and the claimed invention falls within that range, there is a presumption of obviousness.”

Iron Grip Barbell Co. v. USA Sports, Inc., 392 F.3d 1317, 1322 (Fed. Cir. 2004); accord *Lazare Kaplan Int'l, Inc. v. Photoscribe Techs., Inc.*, 628 F.3d 1359, 1380–81 (Fed. Cir. 2010); see also *Tyco Healthcare Grp. LP v. Mut. Pharm. Co.*, 642 F.3d 1370, 1372–73 (Fed. Cir. 2011). A prima facie case of obviousness established by the overlap of prior art values with the claimed range can be rebutted by evidence that the claimed range is “critical” because it “achieves unexpected results.” *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). Here, the claimed doses and range of doses fall within the dosing ranges disclosed by the prior art. As such, there is a presumption that the claimed dosing range and dose amounts are obvious. There is no evidence of unexpected results or criticality for the claimed doses or dosing range.

Determining the particular claimed dosages of pomalidomide from these disclosed ranges of pomalidomide would have required no more than routine optimization of known variables. Optimization that flows from the normal desire of scientists or artisans to improve upon what is already known is generally not patentable. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1366-67 (Fed. Cir. 2007). Due in part to a greater potential for side effects resulting from higher dosage forms, “physicians always seek to prescribe the lowest effective dose of any medication.” *Tyco Healthcare v. Mutual Pharm. Co.*, 642 F.3d 1370, 1371 (Fed. Cir. 2011). Therefore, it would have been obvious to one of skill in the art to optimize the variables necessary for the effective treatment of multiple myeloma using pomalidomide. Additionally, numerous studies in the prior art showed that pomalidomide exhibited encouraging results with respect to anti-multiple myeloma effects when studied in cell cultures or other *in vitro* studies. Based on these studies, it would have been obvious for the POSA to pursue advanced clinical studies, such as Phase I/II studies, that administered pomalidomide to multiple myeloma patients. The procedures and clinical trials for determining the maximum tolerated dose as well as preferred indicated dose for

multiple myeloma drugs was well known and routine. For example, such procedures were already known with respect to thalidomide and with respect to another thalidomide analogue, lenalidomide. It would have been obvious to apply the same or similar procedures to pomalidomide to achieve the claimed dosing.

For example, the person having ordinary skill in the art would have known of dose-determination guidelines in the industry, which would have been considered instructive when seeking to determine a non-toxic, effective dose of pomalidomide. For example, the FDA provides guidance for dose-response and performing studies designed for assessing dose response in life-threatening diseases, such as cancer. FDA Guideline for Industry at 5-6. The FDA Guideline for Industry teaches that “[p]arallel dose-response study designs with placebo, or placebo-controlled titration study designs (very effective designs, typically used in studies of angina, depression, hypertension, etc.) would not be acceptable in the study of some conditions, such as life-threatening infections or potentially curable tumors, at least if there were effective treatments known.” *Id.* at 5. Furthermore, “because in those therapeutic areas considerable toxicity could be accepted, relatively high doses of drugs are usually chosen to achieve the greatest possible beneficial effect rapidly.” *Id.* FDA Guideline for Industry further teaches that “the lack of appropriate salvage therapy for life-threatening or serious conditions with irreversible outcomes may ethically preclude conduct of studies at doses below the maximum tolerated dose.” *Id.* at 7.

In general, the person having ordinary skill in the art would have known that it was routine for chemotherapy drugs such as pomalidomide to conduct a dose-escalation study to determine drug toxicity. For example, phase I clinical trials are often used to estimate the maximum tolerable dose (MTD) of a new drug. Storer at 925; *see also* Fuse at 133; Friedman at

3-4. These trials are typically implemented *ad hoc* with a small patient population where the MTD is found during dose escalation. *Id.*; *see also, e.g.*, Fuse; Rubinstein; EORTC; Friedman; Collins. “Escalation continues until the number of patients experiencing a given degree of toxicity meets some set criterion, at which point the stopping dose or the next lower dose is taken as the MTD.” Storer at 925. Numerous examples of dose-escalations studies would have been known to the person having ordinary skill in the art. For example, Weber 1999 disclosed dose titration of thalidomide to determine the maximally tolerated and effective dose of the drug for the treatment of multiple myeloma. Weber 1999 at 604a. Adjei disclosed a phase I study of an experimental oral cancer drug in patients with solid tumors. Adjei at 1871. Twenty patients with solid tumors received 92 courses of escalating doses given orally twice a day for 7 days out of every 3 weeks. *Id.* Based on observed gastrointestinal toxicity (nausea, vomiting, and diarrhea) the maximum tolerated dose was found to be 350 mg twice daily for subsequent studies. *Id.* Greco disclosed the phase I study of oral etoposide for patients with advanced cancer who were resistant to all standard therapy. Greco at 303. The MTD was determined to be 50 mg/m²/d with myelosuppression as the dose-limiting toxicity. *Id.* at 305-306. *See also, e.g.*, Friedman at 4.

After conducting a dose-escalation study, the person having ordinary skill in the art would have known to consider the MTD when determining dosing for subsequent testing of drug efficacy. Friedman discloses that “[o]nce the MTD is established, the next goal is to evaluate whether the drug has any biological activity or effect and to estimate the rate of adverse effects.” Friedman at 4. The MTD is an important starting point for studies designed to determine efficacy. Smith II discloses that phase I trials “are designed to estimate the MTD, with the usually unstated assumption that this dose would have the greatest chance of therapeutic efficacy with acceptable toxicity. Efficacy of the agent given at MTD would be evaluated in a subsequent

phase II trial.” Smith II at 288. EORTC discloses that “[p]rovided toxicity is not observed at the starting dose, doses are then escalated until side-effects are encountered which are deemed to be dose-limiting. A dose is then selected which is considered safe for phase II trials.” EORTC at 1083. Greco discloses a Phase I study to find the MTD and then performs Phase II studies using the found MTD. Greco at 305-308. Thus, once a MTD is determined, a POSA would take the next logical step and pursue a Phase II clinical study using the MTD, or a lower dose, to determine drug efficacy and arrive at the claimed doses. *See e.g.*, Smith II, EORTC, Rubinstein. It would have been obvious for the person having ordinary skill in the art to follow these routine and known procedures for determining a safe and effective dosing of pomalidomide, and, in particular, the specific doses recited in the claims. The person having ordinary skill in the art would have been motivated to perform these routine procedures to determine the appropriate dosage (e.g., a safe and effective) dosage of pomalidomide.

The claimed dose and dosing range for pomalidomide would have also been obvious in view of the known doses for lenalidomide and thalidomide, in view of the known higher potency of pomalidomide, the knowledge of the person having ordinary skill in the art, and with respect to the known procedures for optimization of dosing amounts (e.g., as explained above). For example, the prior art disclosed dosing for thalidomide and lenalidomide, and it was known to determine optimum doses of thalidomide (and its analogues) in order to balance efficacy with toxicity. *See e.g.*, Thalomid Product; the '325 patent; Durie; Celgene Press Releases; Celgene Annual Report 1999; Palumbo; Rajkumar; Dimopoulos; Singhal; Klausner I; Klausner II.

For example, Palumbo disclosed effective treatment of refractory and relapsed multiple myeloma patients using a thalidomide daily dose of 100 mg per day for a month-long cycle in combination with 40 mg of dexamethasone per day on days 1-4 of the cycle. Palumbo at 399.

Durie evaluated the use of thalidomide at doses between 50 mg and 400 mg/day for the treatment of multiple myeloma with dose escalation based only upon lack of response for the treatment. Durie at 1. Durie also revealed that the “magnitude (% regression) and duration of response do not appear to be influenced by the dose.” *Id.* at 6. In other words, patients on the lowest doses of thalidomide in the study experienced the same efficacy as the patients on higher doses of thalidomide. Rajkumar & Kyle disclosed that higher doses of thalidomide (e.g., 200 mg) are associated with high toxicity and may not yield better response rates than lower doses. Rajkumar & Kyle at 3593. Weber 1999 disclosed dose titration of thalidomide to determine the maximally tolerated and effective dose of the drug for the treatment of multiple myeloma. *See* Weber 1999 at 604a. *See also, e.g.,* Thalomid®, the ’325 patent, Celgene Press Releases, Celgene Annual Report 1999, Rajkumar, Dimopoulos, Singhal, Klausner I, Klausner II, Hus, Knight, Edwards, Adler, Bor, Lipkin.

In addition, June Market Letter disclosed that lenalidomide was more potent than thalidomide and further showed that 5, 10, 25, and 50 mg/day of lenalidomide was administered to patients. June Market Letter at 1. Stirling disclosed that lenalidomide was safely administered to volunteers in single doses of 50 to 400 mg. Stirling at 602. Raje disclosed that the maximum tolerated dose for lenalidomide was 25 mg/day. Raje at 638; *see also* Richardson II at 3063. Moreover, on May 8, 2001 and June 7, 2001, Celgene announced interim data in Phase I/II trials of lenalidomide in multiple myeloma patients, dosing of lenalidomide of 5 mg, 10 mg, 25 mg and 50 mg per day, and administration of lenalidomide to patients with refractory multiple myeloma with encouraging results. Celgene Press Releases (May 8, 2001 and June 7, 2001). *See also, e.g.,* Richardson II at 3063, Dredge 2002, Sorbera, Anderson, Richardson IV, Richardson 2006, Celgene Press Releases, October Market Letter, Richardson I, Marriott 2002.

As explained above, lenalidomide is more potent than thalidomide, and pomalidomide is more potent than lenalidomide, in various anti-MM mechanisms. Therefore, a POSA would have known that smaller doses pomalidomide could have the same efficacy as a larger dose of thalidomide or lenalidomide. As such, a POSA would have expected pomalidomide to have a lower maximum tolerated dose than lenalidomide, and would have been motivated to use smaller doses of pomalidomide than lenalidomide or thalidomide for the treatment of multiple myeloma. It would have been obvious to perform the known dose-response procedures, such as the routine procedures described above, to determine the appropriate dosage of pomalidomide. Especially since the application of such procedures to lenalidomide and thalidomide were already known in the prior art.

It was also known to administer pomalidomide in doses ranging from 1 mg to 10 mg per day. *See e.g.*, Dredge 2003; Marriott 2002; Schey I; Schey II; Schey III. For example, Marriott 2002 reports that “we have also noted profound immunostimulatory effects of oral CC-4047/ACTIMID™ [which is pomalidomide] at 5 mg/day in patients with advanced multiple myeloma (our unpublished observations).” Marriott 2002 at 83. Schey I disclosed the use of pomalidomide in humans with relapsed/refractory multiple myeloma at a dose of between 1 mg/day to 10 mg/day given orally for 4 weeks (28 days). Schey I at 98. Schey I further disclosed that, based on preliminary results, the MTD of pomalidomide was 5 mg/day. *Id.* Schey II also disclosed a phase I study of pomalidomide in relapsed/refractory multiple myeloma in which patients were administered escalating doses starting at 1 mg per day and increasing according to response to 10 mg per day. Schey II at 296. Early responses to pomalidomide were seen at four weeks with 11/18 patients and maximal responses were seen in 12/18 patients up to 10 months after commencing treatment. *Id.* Schey III disclosed that the MTD of pomalidomide

orally was 2 mg/day in the 4 week (28 day) phase I study. Schey III at 291. Thus, the claimed doses of pomalidomide were also disclosed in the prior art.

3. Cyclic Dosing Of Pomalidomide

Claims 1 and 20 of the '262 patent recite administering pomalidomide “for 21 consecutive days followed by seven consecutive days of rest from administration of said compound in a 28 day cycle.” '262 patent at 38:32-34, 39:24-40:1.

Claims 1 and 26 of the '939 patent recite administering pomalidomide “in one or more cycles, each of which comprises administering the compound for a period of time followed by a period of rest.” '939 patent at 39:14-17, 40:32-35. Claim 18 recites “wherein one cycle comprises four to six weeks.” 39:54-55. Claims 19 and 32 further recite “wherein the compound is administered for 21 consecutive days followed by seven consecutive days of rest in a 28 day cycle.” '939 patent at 39:55-57, 40:47-49. Claim 20 recites “wherein the compound is orally administered 4 mg per day on days 1 through 21 of repeated 28-day cycles until disease progression.” '939 patent at 40:1-3.

Claims 1 and 22 of the '428 patent recite administering pomalidomide “for 21 consecutive days followed by seven consecutive days of rest in a 28 day cycle.” '428 patent at 39:17-19, 40:34-35. Claim 16 further recites administering pomalidomide “wherein the compound is orally administered 4 mg per day on days 1 through 21 of repeated 28-day cycles until disease progression.” '428 patent at 40:3-5.

These features are anticipated and rendered obvious by the prior art. For example, it has long been known and practiced to administer chemotherapy drugs, and specifically multiple myeloma drugs, in cycles that include a period for rest, with typical cycles lasting up to four weeks. In particular, it has long been known to administer such drugs in a 28 day cycle, whereby the drug was administered on days 1-21, which was then followed by a 7 day period without the

drug. The person of ordinary skill in the art would have known that in an effort to balance toxicity with efficacy, a conventional dosing schedule calls for episodic application of a cytotoxic drug at or near the maximum tolerated dose, followed by periods of rest to allow normal tissues to recover.

Existing multiple myeloma treatments on the market as of the earliest possible priority date of the '262 patent utilized a cyclical dosing regimen comprising an administration period followed by a rest period to allow for recovery. For example, Alkeran® (melphalan tablets, 2mg) (original approval January 17, 1964) is indicated for “the palliative treatment of multiple myeloma and for the palliation of non-resectable epithelial carcinoma of the ovary.” Alkeran® Label at Indications. The Dosage and Administration states that “[t]he usual oral dose is 6 mg (3 tablets) daily. The entire daily dose may be given at one time. The dose is adjusted, as required, on the basis of blood counts done at approximately weekly intervals. After 2 to 3 weeks of treatment, the drug should be discontinued for up to 4 weeks, during which time the blood count should be followed carefully.” *Id.* at Dosage and Administration.

Other chemotherapeutic drugs were also known to be administered in such cycles. For example, hexamethylmelamine was used in a 21 day/28 day cycle. “Most treatment regimens employ [hexamethylmelamine] at a dose of 4 to 12 mg/kg body weight for 14 days to 21 days, with cycles repeated at 28- to 42-day intervals.” Chemotherapy 1992 at 401-402. The drug etoposide was similarly used in a 21/28 day cycle. “A group of 17 patients received a 7-day infusion of etoposide (schedule A) every 21 days at doses from 30 to 75 mg/m² per day, and a second group of 37 patients a 21-day infusion (schedule B) every 28 days at doses from 18 to 40 mg/m² per day.” Robert at 459. In Samlowski, a total of 26 eligible patients were registered to receive a dose of anti-cancer drug gemcitabine weekly for 3 weeks, followed by a 1 week rest

period. Samlowski at 311. In Lee, treatment was with two drugs during the 21 days of drug administration, which consisted of two cycles of chemotherapy with oral etoposide on days 1-21 and intravenous cisplatin on days 1 and 8 of a 28-day cycle. Lee at 479. Moreover, Oken disclosed four week cycles of the multiple myeloma therapy of melphalan and prednisone (MP) and five week cycles of the multiple myeloma therapy vincristine, carmustine, melphalan, cyclophosphamide, and prednisone (VBMCP). *See* Oken at 1561. Therefore, it was known that different multiple myeloma treatments could have different dosing cycles, including cycles of four to six weeks, as evidenced by Oken. *Id.*

Szelényi teaches that the dosing schedule of chemotherapeutic agents administered in combination therapies for the treatment of multiple myeloma was known to impact both toxicity and efficacy. For example, Szelényi discloses that extending the treatment interval for administration of cyclophosphamide, adriamycin and dexamethasone in the treatment of multiple myeloma decreased the rate of severe thrombocytopenia without compromising efficacy. *See* Szelényi at 108. Accordingly, it was known in the art that higher doses administered by decreasing a treatment-free period in a dosing schedule can increase in toxicity as well as efficacy. Moreover, four week dosing cycles were also known, as evidenced by Szelényi. *See also, e.g.,* Szelényi at 105. *See also, e.g.,* Chu at 292 (“the treatment-free interval between cycles should be the shortest possible time necessary for recovery of the most sensitive normal target tissue, which is usually the bone marrow” because “long intervals between cycles negatively affect dose intensity.”).

The person of ordinary skill in the art would have expected to administer pomalidomide in accordance with standard practices for administration of chemotherapy agents. Furthermore, chemotherapeutic dosing schedules were known in the art to be a result-effective variable with

respect to efficacy and toxicity. The person having ordinary skill in the art would have been motivated to optimize the schedule for administering pomalidomide to treat multiple myeloma through routine experimentation with a reasonable expectation of success in identifying an acceptable balance of efficacy and toxicity. *See In re Boesch*, 617 F.2d 272, 276 (CCPA 1980) (“[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art.”).

Additionally, thalidomide was also known to be administered in daily doses and in monthly cycles. Rajkumar disclosed that thalidomide combined with 40 mg dexamethasone, repeated monthly, was effective against newly diagnosed multiple myeloma. Rajkumar at 168a. Kropff disclosed the combination of thalidomide and dexamethasone administered in a month-long cycle to treat primary refractory or relapsed multiple myeloma. Kropff at 168a. The ’325 patent (Andrulis) disclosed the use of thalidomide for the treatment of melanomas by administering thalidomide on a “therapeutic cycle.” ’325 patent (Andrulis) at 6:3-11. The ’325 patent explained that the term “therapeutic cycle” means a 28-day or other cycle wherein thalidomide or a combination of thalidomide with other anti-melanoma agents is administered to a patient. *Id.* The ’325 patent (Andrulis) further disclosed a clinical trial protocol involving the treatment of melanoma with cycles of thalidomide that lasted for 7, 21, or 28 days depending on the degree of malignancy. *Id.* at 13:1-19. Klausner I disclosed the use of thalidomide daily for 21 days followed by a seven-day washout period in patients with HIV-1. Klausner I at 248. Klausner II also disclosed the use of a seven-day washout period at the end of a cycle of thalidomide treatment in patients with tuberculosis that reduced the negative side effects of thalidomide treatment. Klausner II at 221.

Furthermore, the prior art disclosed that lenalidomide was administered in monthly cycles for the treatment of relapsed or refractory multiple myeloma. Sorbera similarly disclosed that lenalidomide was dosed at 15 mg twice daily, or 30 mg once daily, for 3 weeks with 1 week of rest. Sorbera at 430. Anderson disclosed a phase II trial in which patients were administered 15 mg of lenalidomide twice daily, or 30 mg of lenalidomide once daily, for 3 weeks followed by 7 days of rest. Anderson at 30. *See also, e.g.,* Richardson IV at 104a.

As explained above, the prior art taught that pomalidomide and lenalidomide are thalidomide derivatives with similar mechanism of action and greater potency than thalidomide. Accordingly, it was obvious to substitute pomalidomide for thalidomide or lenalidomide to treat multiple myeloma, and it would have been obvious to apply the dosing cycles already used with thalidomide or lenalidomide when treating with pomalidomide. Furthermore, the determination of the claimed dosing/rest days and the length of the dosing cycle would have been routine optimization to a person of ordinary skill in the art. The person having ordinary skill in the art would have arrived at the claimed dosing schedule recited by routine experimentation and optimization based on the prior art.

4. Administering Dexamethasone or a Second Active Agent

Claims 1 and 20 of the '262 patent recite administering 40 mg of dexamethasone. '262 patent at 38:17-34, 39:9-40:2. Claims 14-15 and 25 of the '262 patent further recite the oral administration of the additional active agent dexamethasone in particular therapeutic doses and on particular days of a monthly dosing schedule. '262 patent at 38:62-67, 40:12-14. Specifically, claims 14 and 25 require that dexamethasone is orally administered in an amount of 40 mg once daily on days 1, 8, 15, and 22 of each 28 day cycle, whereas claim 15 requires that the dexamethasone is administered in an amount of 40 mg once a week of each 28 day cycle. *Id.*

Claim 21 of the '939 patent recites administering a therapeutically effective amount of an additional active agent. '939 patent at 40:4-6. Claim 22 recites administering dexamethasone as the additional active agent and claim 33 recites administering a therapeutically effective amount of dexamethasone. '939 patent at 40:7-8. Claims 23 and 34 specifically recite administering 40 mg of dexamethasone. '939 patent at 40:8-13. Claims 24 and 35 require that dexamethasone is orally administered once daily on days 1, 8, 15 and 22 of a 28 day cycle. '939 patent at 40:11-13, 50:54-57. Claim 25 recites that dexamethasone is orally administered once a week of a 28 day cycle. '939 patent at 40:13-14.

Claim 17 of the '428 patent recites administering a therapeutically effective amount of an additional active agent. '428 patent at 40:6-9. Claim 18 recites administering dexamethasone as the additional active agent and claim 27 recites administering a therapeutically effective amount of dexamethasone. '428 patent at 40:9-10. Claim 19 specifically recites administering 40 mg of dexamethasone. '428 patent at 40:11-12. Claim 20 requires that dexamethasone is orally administered once daily on days 1, 8, 15 and 22 of each 28 day cycle. '428 patent at 40:13-15. Claim 21 recites that dexamethasone is orally administered once a week of each 28 day cycle. '428 patent at 40:16-17.

These features are invalid as anticipated or obvious in view of the prior art. For example, it was well known in the art that dexamethasone was an effective adjunct therapy in the treatment of multiple myeloma. Furthermore, 40 mg was a known dose for dexamethasone used in combination therapies for the treatment of multiple myeloma. Moreover, the prior art showed that IMiDs, including pomalidomide, have anti-multiple myeloma effects, alone and in combination with dexamethasone. For example, Hideshima 2000 disclosed in vitro tests showing that both thalidomide and its analog IMiDs enhance the anti-multiple myeloma activity

of dexamethasone. Hideshima 2000 at 2943, 2946. Hideshima further evaluates the effects of thalidomide and its analogs on multiple myeloma cells in combination with dexamethasone and IL-6. *Id.* Hideshima observes that IMiDs significantly inhibited uptake in multiple myeloma cells, and that dexamethasone further increased the inhibition of proliferation, giving it an “additive effect.” Hideshima at 2946. The authors found that all three IMiDs tested achieved 50% inhibition of DNA synthesis in multiple myeloma cells in vitro, confirming their direct action on tumor cells and suggesting their clinical utility. *Id.* at 2949. Moreover, the IMiDs inhibited the proliferation of dexamethasone-resistant multiple myeloma cells by 50%. *Id.* The authors also concluded that the IMiDs “enhance the anti-MM activity of Dex.” *Id.* at 2943. Because of the disclosures of Muller and Corral II, which together show that pomalidomide is an IMiD, a POSA would know that Hideshima 2000 shows that pomalidomide would enhance the activity of dexamethasone against multiple myeloma.

Thus, the person of ordinary skill in the art would have understood that dexamethasone would have a synergistic effect with pomalidomide in the treatment of multiple myeloma. *See also, e.g.*, Davies at 210; Dredge 2003 at 333; Mitsiades at 4525-4526; Lentzsch 2003 at 41; Richardson III at 118; 2000 Abstracts at 579a (Abstract #2487); Hwu at 22:10-16 and 24:16; Schey II, Knight. The person having ordinary skill in the art would have known to administer pomalidomide with dexamethasone because it was disclosed in the prior art.

Moreover, it was known in the prior art to administer dexamethasone with either thalidomide or lenalidomide. The person of ordinary skill in the art would thus have expected that dexamethasone would have a synergistic effect with pomalidomide in the treatment of multiple myeloma based on the known synergy between dexamethasone and either thalidomide or lenalidomide. Likewise, the person of ordinary skill in the art would have expected to

administer pomalidomide in accordance with known practices for administration of dexamethasone.

Numerous prior art articles showed that thalidomide in combination with dexamethasone had a synergistic effect against multiple myeloma. *See, e.g.*, Rajkumar & Kyle at 3593; Durie at 1 (disclosing that the response “may be enhanced by co-administration of glucocorticoids such as dexamethasone.”); *see also, e.g.*, Rajkumar at 168a; Dimopolous at 994; Lentzsch 2003 at 41; Davies at 210; Richardson III at 118; Schey II at 295. Weber 2000 disclosed clinical efficacy of thalidomide combined with dexamethasone on resistant multiple myeloma. Weber 2000 at 167a. The authors reported that “[r]esponses included 12 of 26 patients (46%) who were resistant to recent programs including high-dose dexamethasone and subsequent thalidomide alone, suggesting synergy.” *Id.* “Response rates were similar for 20 patients with primary refractory disease (55%) and 27 pts. with disease in refractory relapse (48%).” *Id.* The authors concluded that their results “confirm superior activity of thalidomide-dexamethasone for resistant myeloma when compared with thalidomide alone.” *Id.* Furthermore, Weber 1999 also discloses that the combination of thalidomide and dexamethasone is effective for the treatment of multiple myeloma that is primary refractory, as well as multiple myeloma in patients with untested relapse. Weber 1999 at 604a. Weber discloses that multiple myeloma patients effectively treated with a combination of thalidomide and dexamethasone had received previous therapy with thalidomide and autologous stem cell transplant. *See id.* Weber also discloses administration of dexamethasone four days each month in combination with thalidomide to treat multiple myeloma. *Id.*

Dimopolous presents the results of a combination of thalidomide and dexamethasone to treat multiple myeloma in patients who have been previously treated for multiple myeloma, and

not responded to the previous treatment regimens. *See* Dimopolous at 991-92. Likewise, Alexanian reported on a study of multiple myeloma patients who received thalidomide and dexamethasone after intensive previous treatment for multiple myeloma. *See* Alexanian at 1116-1117. Additionally, Palumbo disclosed effective treatment of refractory and relapsed multiple myeloma patients using low-dose thalidomide daily in combination with 40 mg of dexamethasone. Palumbo at 401. Palumbo explained that “[t]halidomide and dexamethasone are a logical combination since they may differ in their action against myeloma.” *Id.* at 402. Palumbo reported that “low-dose thalidomide plus dexamethasone was shown to be extremely well tolerated and highly effective.” Palumbo at 399. In Palumbo, the patients were treated “100 mg [of thalidomide] at bedtime and associated with dexamethasone administered orally at the dose of 40 mg on days 1, 2, 3, and 4 every month.” Palumbo at 400.

Additionally, Rajkumar disclosed that thalidomide combined with 40 mg dexamethasone administered on days 1-4, 9-12, 17-20 (odd cycles) and days 1-4 (even cycles), repeated monthly, was effective against newly diagnosed multiple myeloma. Rajkumar at 168a. Kropff disclosed the combination of thalidomide and dexamethasone administered in a month-long cycle, with dexamethasone administered on days 1-4, 9-12, and 17-20. Kropff at 168a. *See also* Aviles at 23; Dimopoulous at 991. Moreover, Durie disclosed the administration of 40 mg dexamethasone (daily for 4 days, twice a month) for patients having reduced hemoglobin and platelet counts. Durie at 4. *See also, e.g.,* Durie; Hideshima 2000; Rajkumar & Kyle; Mitsiades; Richardson 2001; Richardson 2002; Aviles, Kropff; 2000 Abstracts; Lentzsch 2003; Richardson II; Richardson III; Knight; Kyle at 583, 587. Barlogie 2001 disclosed that response rates in patients with refractory multiple myeloma increased to 50% to 60% when thalidomide was

administered in combination with dexamethasone (20 and 40 mg). Barlogie 2001 at 250, 256-57.

As explained above, the prior art showed that pomalidomide is a thalidomide derivative with similar mechanisms of action and greater potency than thalidomide. A person of ordinary skill in the art would predict that dexamethasone would have the same effect in combination with pomalidomide as it does with thalidomide. Accordingly, it was obvious to substitute thalidomide with pomalidomide to treat multiple myeloma, and it would have been obvious to similarly use pomalidomide in combination with dexamethasone. Additionally, the claimed timing of administration would have simply been accomplished through routine optimization. As discussed above in Section II.C.3, the particular dosing schedule of combination therapies for the treatment of multiple myeloma were known to impact toxicity and efficacy of the active agents. *E.g.*, Szelényi at 108. Accordingly, dosing schedules of chemotherapeutic agents were known result-effective parameters, and determining the optimum dosing schedule that provided efficacy with acceptable or minimal toxicity would have simply been a matter of routine experimentation for one of ordinary skill in the art.

5. Treating Relapsed, Refractory, Or Relapsed And Refractory Multiple Myeloma

Claims 2, 4-5, and 29 of the '262 patent further recite that the multiple myeloma being treated is relapsed, refractory, or relapsed and refractory multiple myeloma. '262 patent at 38:35-36, 38:39-42, 40:22-23. Claim 1 of the '939 patent further recites that the multiple myeloma is relapsed, refractory, or relapsed and refractory multiple myeloma. '939 patent at 38:65-39:20. Similarly, claim 1 of the '428 patent further recites that the multiple myeloma is relapsed, refractory, or relapsed and refractory multiple myeloma. '428 patent at 39:2-21.

These features are invalid as anticipated or obvious in view of the prior art. It was known that IMiDs such as pomalidomide were effective against refractory and relapsed MM. For example, Hideshima 2000 disclosed the use thalidomide and of IMiDs to treat refractory MM, demonstrating a 50% reduction in proliferation of Dex-resistant MM cells in vitro. Hideshima 2000 at 2946, 2949. Hideshima 2000 teaches that “[t]hese studies demonstrate clinical activity of Thal against MM that is refractory to conventional therapy and delineate mechanisms of anti-tumor activity of Thal and its potent analogs (immunomodulatory drugs [IMiDs]). ... Thal and the IMiDs enhance the anti-MM activity of Dex [dexamethasone].” Hideshima 2000 at Abstract. As explained above, a person having ordinary skill would have known from Corral II and Muller that IMiDs in Hideshima 2000 included pomalidomide. Moreover, Davies disclosed that “results suggest that Thal and new analogues may not only be useful in the treatment of refractory/relapsed disease, but also be effective in the maintenance of minimal residual disease after transplantation by enhancing NK-cell-mediated anti-MM cell immunity.” Davies at 216.

Furthermore, pomalidomide was also known to be effective in treating relapsed and/or refractory multiple myeloma. For example, Schey I discloses a Phase I study using pomalidomide (i.e. CC4047) for the treatment of relapse/refractory multiple myeloma. *See* Schey I at 98. Patients were reported to have undergone chemotherapy, autologous stem cell transplantation and/or prior thalidomide treatment. *Id.* Schey II reports that thalidomide analogues, including pomalidomide, have been developed to “improve efficacy and reduce toxicity,” and that two in particular, including pomalidomide, are in clinical development with promising results. *See* Schey II at 295. Schey II describes the clinical studies of pomalidomide in patients with relapsed or refractory myeloma and reports that the results are “very encouraging.” *Id.* at 296; *see also, e.g.,* Dredge/Marriott at 433-34 (“[Pomalidomide] has

recently been found to possess an acceptable safety profile in a phase I trial for relapsed/refractory multiple myeloma.”); Dredge 2003 at 333; Schey Report at 1; Schey III at 291; Celgene Press Release (July 8, 2002); Celgene Press Release (June 25, 2002); Lentzsch 2001 at 473a; 2000 Abstracts at 579a.

Thus, the person of ordinary skill in the art would have known to use pomalidomide to treat relapsed and refractory myeloma because it was disclosed in the prior art. Moreover, the prior art also disclosed the treatment of refractory and relapsed multiple myeloma with thalidomide. For example, the prior art disclosed using thalidomide for the treatment of patients with multiple myeloma who had received previous therapies, and specifically as salvage therapy after numerous other lines of therapy. By 2001, “thalidomide [was] considered as part of standard therapy for relapsed myeloma.” Rajkumar & Kyle at 3593. Singhal also showed impressive response rates in patients with refractory and relapsed multiple myeloma. Rajkumar & Kyle at 3593. *See also* Zangari 2002 at 1168 (“thalidomide has proven activity in refractory multiple myeloma (MM)...”).

Singhal disclosed treating MM patients with thalidomide where 90% of the patients in this study had failed previous autologous stem-cell transplantation. Singhal at 1566. Singhal’s study showed that thalidomide is active against advanced myeloma in these patients who had previously been treated with stem-cell transplantation and still demonstrated disease progression. *Id.* at 1565, 1566. *See also* Singhal at 1571 (“thalidomide is active against multiple myeloma, even in patients who relapsed after repeated cycles of high-dose chemotherapy. Larger studies of thalidomide, its analogues, and other inhibitors of angiogenesis are therefore warranted in patients with myeloma and other cancers. We are currently evaluating thalidomide in combination with chemotherapy for patients with newly diagnosed multiple myeloma.”).

Dimopoulos describes treating patients with refractory multiple myeloma with thalidomide and dexamethasone. Dimopoulos reports daily administration of an oral dose of thalidomide at 200 mg (with subsequent dose escalation) and an oral dose (20 mg/m²) of dexamethasone for four days on day 1-4, 9-12, 17-20, followed by monthly dexamethasone for four days. Dimopoulos at 991.

Palumbo, Durie and Barlogie 2001 likewise disclosed the treatment of refractory and relapsed myeloma with thalidomide in combination with dexamethasone. Palumbo at 399; Durie at 2; Barlogie 2001 at 250, 257. Palumbo reports daily administration of an oral dose of thalidomide at 100 mg and an oral dose of (40 mg) of dexamethasone on days 1-4 every month. Palumbo taught that low-dose thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma and that “[t]wenty-six patients received thalidomide after one line of therapy, 21 after two and 30 after three. Among those receiving high-dose chemotherapy, 17 were in first untested relapse, 18 in second untested relapse and 2 were in resistant relapse. Of those treated with conventional chemotherapy, 4 had primary resistance, 19 were in resistant relapse and 17 in untested relapse.” Palumbo at 400. Durie evaluated thalidomide at doses between 50 mg and 400 mg/day with dose escalation based only upon lack of response in myeloma patients. The study disclosed that “[a]ll patients had received prior therapy of some sort” before entering the study and had relapsing or progressive multiple myeloma.” Durie at 3, 1. Durie also disclosed that “[l]ow dose thalidomide is generally well tolerated and can induce excellent remission in 25% of relapsing or refractory myeloma patients.” *Id.* at 1. Durie stated that “[t]he benefit of thalidomide was particularly evident in patients who had previously received stem cell transplants.” *Id.* at 4. Barlogie 2001 discloses that “[s]everal single agent thalidomide trials in refractory disease showed an overall response rate (PPR \geq 50%) of 36%

among 352 patients with available information. The addition of dexamethasone increases the response rate beyond 50%.” Barlogie 2001 at 256-57.

The other kinds of previous therapy—thalidomide, 3-(4-amino-1-oxo-1,3-dihydroisoindol-2-yl)-piperidine-2,6-dione, a proteasome inhibitor—were also known therapies for MM, and these claims merely add that these known treatments for MM would occur prior to the use of pomalidomide for MM. For example, Hideshima 2001 taught that “[p]roteasome inhibitors represent a novel potential anticancer therapy” based on a study that “demonstrate[s] that the proteasome inhibitor PS-341 directly inhibits proliferation and induces apoptosis of human MM cell lines and freshly isolated patient MM cells. . . .” Hideshima 2001 at 3071. Weber 1999 disclosed that patients with resistant myeloma who did not respond to initial treatment with thalidomide “were treated with a combination of their previously maximally tolerated dose of thalidomide and intermittent dexamethasone.” Weber 1999 at 604a. Weber reported that “[partial response] was achieved in 4 of 10 pts. (40%) with primary resistant disease and 5 of 16 pts. (31%) with resistant relapse for overall response rates of 50% for primary refractory disease and 41% for myeloma in refractory relapse.” *Id.*

As explained above, the prior art showed that pomalidomide is a thalidomide derivative and that pomalidomide was a highly potent treatment for multiple myeloma compared to thalidomide. Accordingly, the person having ordinary skill in the art would have understood that if thalidomide was effective in the treatment of relapsed or refractory multiple myeloma, pomalidomide should be even more effective due to its increased potency and direct action on multiple myeloma cells. The person having ordinary skill in the art would have been motivated to use this potent therapy in the treatment of multiple myeloma, including in the treatment of

relapsed and refractory multiple myeloma. It was obvious to substitute thalidomide with pomalidomide to treat relapsed and refractory multiple myeloma.

6. Administering Orally In The Form Of A Capsule In Various Dosages

Claims 16, 18 and 26 of the '262 patent further recite that pomalidomide is administered orally in the form of a capsule in various dosages. '262 patent at 39:1-2, 39:5-6, 40:15-16. Specifically, claim 16 requires the compound to be administered as a capsule, and claims 18 and 26 require the compound to be administered in a capsule of 1 mg, 2 mg, 3 mg, or 4 mg. *Id.*

Claims 13-14, 17 and 30-31 of the '939 patent further recite that pomalidomide is administered orally in the form of a capsule in various dosages. '939 patent at 39:44-47, 39:52-53, 40:43-46. Specifically, claims 13 and 30 require that pomalidomide is administered orally. '939 patent at 39:44-45, 40:43-44. Claims 14 and 31 require the compound to be administered as a capsule, and claim 17 requires the compound to be administered in a capsule of 1 mg, 2 mg, 3 mg, or 4 mg. '939 patent at 39:46-47, 40:45-46, 39:52-53.

Claims 12-13, 15 and 25-26 of the '428 patent further recite that pomalidomide is administered orally in the form of a capsule in various dosages. '428 patent at 39:43-46, 40:1-2, 40:41-44. Specifically, claims 12 and 25 require that pomalidomide is administered orally. '428 patent at 39:43-44, 40:41-42. Claims 13 and 26 require the compound to be administered as a capsule, and claim 15 requires the compound to be administered in a capsule of 1 mg, 2 mg, 3 mg, or 4 mg. '428 patent at 39:45-46, 40:43-44.

These features are anticipated and rendered obvious by the prior art. The discussion above in Section II.C.2 is incorporated herein by reference. The discussion below Section II.C.7 is incorporated herein by reference.

7. **Administration Of Pomalidomide With Particular Inactive Ingredients**

Claims 19 and 27 of the '262 patent further recites the administration of pomalidomide in capsules with particular inactive ingredients: mannitol and pre-gelatinized starch. '262 patent at 39:7-8, 40:17-18. Claim 16 of the '939 patent further recites the administration of pomalidomide in capsules with particular inactive ingredients: mannitol and pre-gelatinized starch. '939 patent at 39:50-51. Claim 14 of the '428 patent further recites the administration of pomalidomide in capsules with particular inactive ingredients: mannitol and pre-gelatinized starch. '428 patent at 39:47-48.

These features are anticipated and obvious in view of the prior art. A person of ordinary skill in the art would have known to administer pomalidomide in the form of a capsule because it was disclosed in the prior art. For example, the '517 patent discloses a method of reducing undesirable levels of TNF- α in a mammal comprising administering pomalidomide (1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline). '517 patent at 12:8-10. The '517 patent taught that pomalidomide can be prepared in "[o]ral dosage forms," including capsules and tablets. *Id.* at 5:62-63. The '517 patent explained that the capsules can contain the compound and at least one pharmaceutically acceptable carrier, diluent or excipient. *Id.* at 6:4-6. Examples of suitable excipients include, *inter alia*, mannitol and starch. *Id.* at 6:15-24. *See also, e.g.,* '471 patent at 8:35-50 (disclosing that pharmaceutical compositions of pomalidomide may be in the form of a capsule and suitable excipients include mannitol and starch). In addition, Hwu disclosed compositions comprising pomalidomide for the treatment of cancer. Hwu at 19:12-14. Hwu further disclosed that these compositions could be administered in tablet or capsule form including excipients. *Id.* at 32:7, 32:29-33:5. Suitable excipients include fillers such as mannitol and pre-gelatinized starch. *Id.* at 36:7-10. The '291 patent disclosed administration of

pomalidomide to treat undesired angiogenesis that occurs in blood borne tumors and leukemia. *See* '291 patent at claims 65 and 77. The '291 patent disclosed that “[f]ormulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient.” *Id.* at 13:36-39. WO 98/03502 disclosed that pharmaceutical compositions of pomalidomide could be in the form of a capsule and suitable excipients included mannitol and starch. WO 98/03502 at 12:16-13:4.

Moreover, it was obvious to administer pomalidomide similar to the known administration method for thalidomide, which was orally as a capsule. For example, Palumbo disclosed administering thalidomide in capsule form for oral administration. Palumbo at 400; *see also, e.g.*, Thalomid Product (thalidomide was sold in a capsule that included inactive ingredients). Rajkumar likewise disclosed the oral administration of thalidomide. Rajkumar at 168a. Additionally, the '517 patent taught the use of thalidomide derivatives that can be prepared in “[o]ral dosage forms,” including capsules and tablets. '517 patent at 5:62-63.

Thus, the person of ordinary skill in the art would have also known to administer pomalidomide in capsules with particular inactive ingredients such as mannitol and pre-gelatinized starch because it was disclosed in the prior art. Likewise, mannitol and pre-gelatinized starch are two of the most common formulation excipients and are well-known for their use in oral dosage forms. For example, the '177 patent disclosed “a compressible starch, useful as a . . . binder-diluent for capsules, which consists essentially of a free-flowing compressible starch powder.” '177 patent at 3:52-56. The '177 patent further disclosed “an admixture of the above compressible starch and an effective amount of a wet granulation binder, e.g., pregelatinized starch.” *Id.* at 4:4-7. The '177 patent suggested that the properties of the

binder—compressible and free-flowing—make it suitable for use in conventional dry dosage capsule-filling methods. *See id.* at 1:34-41.

Moreover, determining recipes for inactive ingredients is no more than routine optimization of known variables. A person of ordinary skill in the art would have knowledge of various recipes for creating capsules with inactive ingredients, any number of which would form a useable capsule. There is no teaching away from using these ingredients in a capsule with pomalidomide. Inclusion of these excipients is routine use of known materials for their known purpose, and would have been obvious to the person of ordinary skill in the art.

8. Treating A Patient That Has Received Previous Therapy

Claims 6-9 of the '262 patent further specify that the patient has received previous therapy, the patient has demonstrated disease progression on the previous therapy, and where the previous therapy was treatment with thalidomide, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, a proteasome inhibitor, stem cell transplantation, or a combination thereof. '262 patent at 38:43-53.

Independent claim 26 and dependent claims 2-5 and 27 of the '939 patent further specify that the patient has received previous therapy, the patient has demonstrated disease progression on the previous therapy, and where the previous therapy was treatment with thalidomide, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, a proteasome inhibitor, stem cell transplantation, or a combination thereof. '939 patent at 40:15-34, 39:21-29, 40:36-37.

Independent claims 1 and 22 and dependent claims 2-5 and 23 of the '428 patent further specify that the patient has received previous therapy, the patient has demonstrated disease progression on the previous therapy, and where the previous therapy was treatment with thalidomide, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, a proteasome

inhibitor, stem cell transplantation, or a combination thereof. '428 patent at 39:1-21, 40:18-35, 39:22-30, 40:36-37.

These features are anticipated and rendered obvious by the prior art. As explained above, the prior art showed that pomalidomide was a more potent treatment for multiple myeloma than thalidomide. Accordingly, it was obvious to substitute pomalidomide for thalidomide to treat patients who had received prior therapies and/or had demonstrated disease progression on the previous therapy. The person of ordinary skill in the art would have understood that if thalidomide was effective in the treatment of relapsed or refractory multiple myeloma (which are by definition, following previous therapy and demonstrating disease progression), pomalidomide should be even more effective due to its increased potency and direct action on multiple myeloma cells. The person of ordinary skill in the art would have been motivated to use this potent therapy in the treatment of multiple myeloma, including in the treatment of relapsed and refractory multiple myeloma. The discussion above in Section II.C.5 is incorporated herein by reference.

9. Treating Patients Having A Particular Age

Claims 6-7 of the '939 patent further recite treating a patient who is "65 years of age or younger," or "wherein the patient is older than 65 years." '939 patent at 39:30-33. Similarly, claims 6-7 of the '428 patent further recite treating a patient who is "65 years of age or younger," or "wherein the patient is older than 65 years." '428 patent at 39:31-34.

These features are anticipated and rendered obvious by the prior art. The prior art demonstrated the use of thalidomide to treat multiple myeloma in patients of a broad range of ages. Specifically, the prior art teaches treating patients who are 65 years or older, and treating patients who are 65 years of age or younger. Durie, for example, reported the administration of thalidomide to patients where the "median age was 56 years with a range of 36-77 years." Durie

at 3. Moreover, Hus reported treating multiple myeloma patients as young as 32 and as old as 79. Hus at 405. Hus provides additional motivation to treat patients over 65 with pomalidomide, as one of ordinary skill in the art would expect pomalidomide and thalidomide to be effective in similar demographic groups, and thalidomide was known to treat patients over 65. Additionally, Singhal teaches treating multiple myeloma with thalidomide monotherapy in 84 patients, of whom 32 were over 60 years old. Singhal at 1566. The person having ordinary skill in the art would recognize that 60 and 65 are similar ages, and would have found it obvious to administer the drug to patients over 65 based on Singhal's disclosed treatment of patients over 60. As explained above for the independent claims, the prior art showed that pomalidomide is a thalidomide derivative with similar mechanisms of action and greater potency than thalidomide. Accordingly, it was obvious to substitute pomalidomide for thalidomide to treat multiple myeloma in a patient who is (1) 65 years of age or younger or (2) older than 65 years.

Moreover, Schey I discloses that in a Phase I dose escalation study for pomalidomide in relapsed/refractory multiple myeloma, fifteen (15) patients entered the study with a median age of 67, ranging from 55 years to 81 years. Schey I at 98. Thus, as pomalidomide had already been administered to patients older and younger than 65 years old in a Phase I study where pomalidomide was found to have "an acceptable toxicity profile with anti-tumor activity" in relapsed/refractory multiple myeloma, the limitations of these claims requiring patients older or younger than 65 years old would be obvious to the person of ordinary skill. *Id.*

Furthermore, the person having ordinary skill in the art would understand that the cellular mechanisms involved in pomalidomide monotherapy for treating multiple myeloma would occur at any age. It would have been obvious to consider the same or similar treatment regardless of age. The age of the patient to be treated in accordance with the claimed method is not inventive

in any way. There was no teaching away from administering pomalidomide to patients above or below a certain age cutoff, and there is no evidence of any unexpected results relative to the prior art that would make such administration non-obvious.

10. Administration Of Pomalidomide As A Free Base

Claims 12 and 29 of the '939 patent further recite that pomalidomide is administered as a free base. '939 patent at 39:42-43, 40:41-42.

This limitation is anticipated and rendered obvious by the prior art. The prior art demonstrated that one of ordinary skill in the art would know that pharmaceutical compounds can be administered in the form of a free base. For example, the '517 patent disclosed pomalidomide in Formula I when both X and Y are C=O, as well as other derivatives of thalidomide. '517 patent at 4:25-32. The '517 patent disclosed the structure of pomalidomide in Formula I of the specification and in claim 1 in non-protonated, free base form. *Id.* at 4:25-32, 11:2-7. Furthermore, the '517 patent taught that “[t]he present invention also pertains to the physiologically acceptable non-toxic *acid* addition salts of the compounds of Formula I.” *Id.* at 5:53-55 (emphasis added).

The '291 patent also teaches that the compound may be a free base. In particular, the '291 patent teaches administration of pomalidomide (3-aminothalidomide) to treat undesired angiogenesis that occurs in blood borne tumors. *See* '291 patent at claim 65. The '291 patent discloses the chemical structure of pomalidomide [i.e., pomalidomide as a free base]. One of ordinary skill in the art would be motivated to treat multiple myeloma patients with the free base of pomalidomide.

In general, administration of a known drug as a free base was known to those of ordinary skill in the art. There is no teaching away from the use of pomalidomide free base, and there is no evidence of any unexpected results from administering pomalidomide as a free base.

Determination of whether to utilize the free base of a drug or not, and carrying out that process was routine optimization to a person of ordinary skill in the art. Thus, it would have been obvious to administer pomalidomide as a free base.

The discussion above in Section II.C.2 is incorporated herein by reference.

11. Objective Indicia of Non-Obviousness

Courts have identified at least seven objective indicia of non-obviousness: (1) the commercial success of the invention; (2) a long-felt but unsolved need; (3) failure of others to produce the invention; (4) surprising or unexpected results (or properties) of the invention; (5) licenses showing industry respect for the invention; (6) skepticism of skilled artisans before the invention; and (7) copying by others. Evidence of objective evidence must be considered in conducting an obviousness analysis. *In re Cyclobenzaprine Hydrochloride*, 676 F.3d 1063, 1080 (Fed. Cir. 2012). However, such evidence with any such showing must be commensurate in scope with the claims. That is, there must be a nexus between the asserted indicia, such as unexpected result, and the claimed invention. *Wyers v. Masterlock*, 616 F.3d 1231, 1246 (Fed. Cir. 2010); *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952 (Fed. Cir. 2014). Defendants contend that no objective indicia weigh in favor of non-obviousness with respect to the asserted claims of the Zeldis patents. Defendants note that it is Plaintiff's burden to come forward with any purported evidence of objective indicia of non-obviousness, if any, on which it intends to rely. Celgene has not yet alleged in this case any objective indicia of non-obviousness.

With respect to unexpected results, Defendants are not aware of any evidence of any unexpected results of the alleged inventions of the Zeldis Patents. As an initial matter, "[u]expected results that are probative of nonobviousness are those that are 'different in kind and not merely in degree from the results of the prior art.'" *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013). In order for alleged unexpected results to be probative of

non-obviousness, it must be proved that “there actually is a difference between the results obtained through the claimed invention and those of the prior art,” and that “the difference actually obtained would not have been expected by one skilled in the art at the time of invention.” *In re Freeman*, 474 F.2d 1318, 1324 (C.C.P.A. 1973) (citations omitted). Further, the Court must consider “what properties were expected.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007).

During prosecution of the '074 application (which issued as the '262 patent) and '728 application (which issued as the '939 patent), Celgene alleged unexpected results of the claimed methods. For example, Celgene argued that “small differences in structure of pomalidomide from thalidomide mean very important differences in terms of side effect profiles, efficacy and potency.” See Celgene’s response filed December 10, 2010 during prosecution of the '074 application, at 11. Additionally, Celgene argued that “studies showed the impressive activity of pomalidomide in patients who were refractory to other agents including thalidomide.” *Id.* Celgene further argued that a regimen of pomalidomide and dexamethasone “exhibits surprisingly fewer toxicities” and is “significantly active in refractory myeloma.” See Celgene’s response filed December 20, 2011 during prosecution of the '074 application, at 10. Celgene argued that the claimed therapy showed “unexpected results” for relapsed or refractory multiple myeloma, and that it was unexpected that “pomalidomide would be able to treat multiple myeloma that is relapsed after or refractory to prior treatment.” *Id.*; see also Celgene’s response filed October 8, 2013 during prosecution of the '728 application, at 7. Additionally, Celgene alleged, by way of Dr. Thakurta, that it was “surprising” that “the resistance of multiple myeloma cells to pomalidomide and lenalidomide is not reciprocal,” that “[u]nexpectedly, pomalidomide is able to exert its activities with a lesser amount of the target, which likely

explains its therapeutic activity in resistant myeloma,” and that “the results of the studies for treating relapsed and/or refractory multiple myeloma with single-agent pomalidomide would have been unexpected and surprising at the time the claimed invention was made.” Thakurta Declaration dated at October 7, 2013 filed during prosecution of the ’728 application, ¶ 7, at 3.

Defendants contend that nothing presented during the prosecution history of any of the Zeldis Patents constitutes an unexpected result of the claim subject matter.

Celgene has not shown that the claimed methods show surprising or unexpected results probative of non-obviousness. For instance, one of ordinary skill knew that Celgene admitted that the IMiDs (including pomalidomide) “have shown none of thalidomide’s long list of troubling side effects,” and that the IMiDs would replace thalidomide for treatment of multiple myeloma. Knight at 3. One of ordinary skill also knew that pomalidomide “very potently inhibits myeloma cell growth,” which “offers great promise for the treatment of multiple myeloma.” D’Amato 2001 at 599-600. One of ordinary skill further knew that the IMiDs (including pomalidomide) “represent a new treatment paradigm targeting both the tumor cell and the microenvironment to overcome classical drug resistance and achieve improved outcome in MM.” Hideshima Abstract at 304a. Further, one of ordinary skill knew that pomalidomide was by far the most active IMiD in assays that measured TNF- α inhibitory activity and sensitivity to multiple myeloma cell lines. *See, e.g.*, Muller at 1629; Lentzsch 2002 at 2304; Gupta at 1950; Dredge 2001 at Abstract, 4918-19; Davies at 210, 214, Fig. 6; Hideshima 2000 at 2945; and D’Amato 2001 at 598-599. Given the prior art disclosure of pomalidomide’s similar mechanism of action and higher potency than thalidomide, one of ordinary skill would have reasonably expected pomalidomide to be more effective than thalidomide for treating patients with multiple myeloma, and routine optimization efforts would have led to the claimed dosing.

Furthermore, “when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.” *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006). Celgene has not shown that any alleged properties of pomalidomide were surprising or unexpected in view of the closest prior art. For example, both lenalidomide and thalidomide were known to have synergistic or enhanced effectiveness when combined with dexamethasone. *See e.g.*, Hideshima at 2943; Davies at 210; Dredge 2003 at 333; Mitsiades at 4525-26; Lentzsch at 41; Rajkumar & Kyle at 3593; Durie at 1; Rajkumar at 168a; Dimopolous at 994; Lentzsch 2003 at 41; Davies at 210; Schey II at 295; Richardson I at 775a; Richardson II at 3067; Richardson III at 118; Celgene Press Release (May 8, 2001); Celgene Press Release (June 7, 2001). Additionally, lenalidomide was known to be an effective treatment in patients with relapsed or refractory multiple myeloma, such as in patients with resistance to thalidomide. *See, e.g.*, Marriott 2001 at 679; Sorbera at 430; Anderson at 30; Richardson IV at 104a; Hideshima 2000 at 2943, 2949; Davies at 216. Celgene has not shown that there would have been an expectation that pomalidomide would not behave in the manner described. To the contrary, the person having ordinary skill in the art would have expected pomalidomide to be active in patients who were refractory to other agents and to be enhanced by administration with dexamethasone, especially given its similar structure to lenalidomide, which also exhibited these properties.

Likewise, it was known that slight variations in chemical structure can be sufficient to overcome resistance. *See, e.g.*, Shah et al., “Multiple BCR-ABL kinase domain mutations confer polyclonal resistance to the tyrosine kinase inhibitor imatinib (STI571) in chronic phase and blast crisis chronic myeloid leukemia,” *Cancer Cell* 2:117-125 (August 2002); Shannon et al., “Resistance in the land of molecular cancer therapeutics,” *Cancer Cell* 2:99-102 (August 2002);

Hideshima et al., “Molecular mechanisms of novel therapeutic approaches for multiple myeloma,” *Nature Review: Cancer* 2:927-937 (December 2002); John C. Lukesh III, et al. “Vinblastine 20’ Amides: Synthetic Analogues That Maintain or Improve Potency and Simultaneously Overcome Pgp-Derived Efflux and Resistance,” *J. Med. Chem.*, 60(17):7591–7604 (2017). EntreMed in their press release indicated that pomalidomide and lenalidomide “[a]lthough chemically related,” have shown “a different spectrum of responses.” *See, e.g.*, EntreMed Press Release (August 7, 2001). Thus, it would not have been expected that patients with resistance to lenalidomide would also be resistant to pomalidomide. To the contrary, resistance to lenalidomide would have suggested to the person having ordinary skill in the art to use compounds having slightly different chemical structures in order to overcome the resistance. *Id.* Celgene’s alleged unexpected results are moreover not commensurate with the scope of the claims. For example, the claims do not all require use with dexamethasone or treatment of relapsed or refractory multiple myeloma, nor do the claims require previous treatment with lenalidomide.

Moreover, it is clear that the investigators who were part of the trials for pomalidomide expected before the trials were initiated that pomalidomide would demonstrate effectiveness in patients with lenalidomide resistivity. *See, e.g.*, Lacy et al., “Pomalidomide (CC4047) Plus Low-Dose Dexamethasone as Therapy for Relapsed Multiple Myeloma,” *J. of Clinical Oncology* 27(30):5008-5014 (2009). For example, the physicians conducting studies on pomalidomide initiated the study because they were “specifically looking at responses among patients refractory to other novel agents, including other IMiDs.” *Id.* at 5009. Indeed 62% of the patients had a previous IMiD therapy, including 21 patients with prior lenalidomide therapy. *Id.* at 5010. The individuals designing this study clearly expected pomalidomide to be successful in these

patients. The person having ordinary skill in the art would not have considered the activity of pomalidomide in MM refractory to other IMiDs unexpected because trials were specifically designed to study this in patients, and it would not be ethical to design clinical trials in patients if these trials are expected to fail. *See, e.g.*, Kardinal CG, “Ethical issues in cancer clinical trials,” J. La. State Med. Soc. 146(8):359-61 (August 1994) at 359 (“Physicians involved in a randomized trial ... would not recommend that the patient enter investigational therapy unless he thought it might be helpful.”). Thus, the person having ordinary skill in the art would not have expected any different result than what was achieved.

Furthermore, for alleged unexpected results to be probative of non-obviousness, those results must arise from the novel element(s) of the claimed subject matter, and not from elements of the claimed subject matter that are disclosed in the prior art. *See In re Kao*, 639 F.3d 1057, 1073-74 (Fed. Cir. 2011). Here, it is indisputable that pomalidomide and many other elements of the claimed subject matter were disclosed in the prior art. Accordingly, to the extent that the alleged unexpected results arise from pomalidomide itself or from other aspects of the claimed subject matter disclosed in the prior art, those alleged unexpected results are not probative of non-obviousness.

Defendants contend that despite any purported commercial success of Pomalyst®, the Zeldis Patents are invalid as obvious. With respect to commercial success, Defendants are not aware of any evidence of the commercial success of the alleged inventions of the Zeldis Patents. Furthermore, any purported success of Pomalyst® has no nexus to the subject matter claimed by the Zeldis Patents. To be probative of nonobviousness, there must be a nexus between the commercial success and the novel features of the patented invention. *AstraZeneca LP v. Breath Ltd.*, 2015 WL 777460 (D.N.J. Feb. 13, 2015) (aff’d *AstraZeneca LP v. Breath Ltd.*, 603 Fed.

Appx. 999 (Fed. Cir. 2015). “[I]f the commercial success is due to an unclaimed feature of the [invention], the commercial success is irrelevant.” *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006). Likewise, “if the feature that creates the commercial success was known in the prior art, the success is not pertinent.” *Id.* If a patentee can establish a nexus between commercial success and the patented invention, the challenger then bears the burden to show that the success was due to advertising or other extraneous factors. *See, e.g., J.T. Eaton & Co. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997).

Any profits or revenue associated with sales of Pomalyst® do not demonstrate the non-obviousness of the claimed subject matter. For example, any such profits or revenue have no nexus to the claimed subject matter at least because these are attributable to other non-claimed features, such as Celgene’s marketing activities, and/or to non-novel features of the Zeldis Patents. Additionally, any sales of Pomalyst® alone are not indicative of the success of claimed elements that require administration with dexamethasone or other additional active agent. Furthermore, commercial success is not significantly probative if others in the field would have been deterred or inhibited from placing the product on the market by other forces, such as rights to exclude others from practicing the invention and/or impediments such as the burdens of regulatory approval (e.g. FDA approval). *Merck & Co., Inc. v. Teva Pharma. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005). The Zeldis Patents are similar to and not patentably distinct from other prior patents claiming pomalidomide (e.g., the ’471 patent and U.S. Patent Nos. 8,158,653, 6,476,052, 5,635,517) and other patents that block the commercial use of Pomalyst®, such as patents covering REMS. Any purported success is attributable to those patents and not to the Patents-in-Suit. Likewise, any purported success is not tied to the alleged novelty of the

Patents-in-Suit, since, for example, it is attributable to the used of pomalidomide, which has already been claimed in other patents as stated above.

Defendants contend that no other objective evidence supports a finding of non-obviousness. Defendants are not aware of any long felt need supposedly resolved by the Zeldis Patents, any failure of others to achieve the subject matter claimed by the Zeldis Patents, or any skepticism with respect to the subject matter claimed by the by the Zeldis Patents. Defendants are not aware of any licensing of the Zeldis Patents or any copying of the subject matter claimed by the Zeldis Patents that may be reflective of the non-obviousness of the Zeldis Patents. Defendants are not aware of any recognition in the industry for the claimed subject matter of the Zeldis Patents or any acquiescence to the validity of the claims of the Zeldis Patents. Further, Defendants are not aware of any evidence of the required nexus. Even if there were any evidence of these objective indicia of non-obviousness and the required nexus, the evidence of obviousness is sufficiently strong that, when all the evidence is considered together, the claimed subject matter would have been obvious. *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (“While secondary considerations must be taken into account, they do not necessarily control the obviousness determination.”); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007). *See also Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007) (holding that the objective considerations of non-obviousness presented, including substantial evidence of commercial success, praise, and long-felt need, were inadequate to overcome a strong showing of obviousness).

Defendants reserve the right to amend and/or supplement these responses as discovery proceeds in this case and once Celgene has provided its responsive validity contentions.

Defendants reserve the right to rebut any claims or evidence of objective indicia of non-obviousness raised by Celgene.

D. Invalidity Based on Obviousness-Type Double Patenting

“The doctrine of double patenting is intended to prevent a patentee from obtaining a time wise extension of [a] patent for the same invention or an obvious modification thereof.” *In re Basell Poliolefine Italia S.P.A.*, 547 F.3d 1371, 1375 (Fed. Cir. 2008). “The judicially-created doctrine of obviousness-type double patenting cements that legislative limitation by prohibiting a party from obtaining an extension of the right to exclude through claims in a later patent that are not patentably distinct from claims in a commonly owned patent.” *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 967 (Fed. Cir. 2001). The doctrine applies to patents or applications that have at least one common inventor, or that are commonly owned. *In re Hubbell*, 709 F.3d 1140, 1146 (Fed. Cir. 2013). An obviousness-type double-patenting analysis is analogous to an obviousness analysis under 35 U.S.C. § 103. *AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1378 (Fed. Cir. 2014).

1. The Asserted Claims of the Zeldis Patents Are Invalid Over Claims of the '471 Patent, '653 Patent, '052 Patent, and '517 Patent.

The Asserted Claims of the Zeldis Patents are invalid for obviousness-type double patenting (“ODP”) over at least claims 1-15 and 16-26 of the '471 patent, claims 1-2 of U.S. Patent No. 8,158,653 (“the '653 patent”), claims 1-14, 16-19, and 20-28 of U.S. Patent No. 6,476,052 (“the '052 patent”), and/or claims 1, 7, and 8 of U.S. Patent No. 5,635,517 (“the '517 patent”), alone or in combination with one or more of the references listed above. For example, claims 1-15 and 16-26 of the '471 patent recited methods of treatment using pomalidomide, including for oncogenic or cancerous conditions. Claims 1-2 of the '653 patent are directed to oral dosages of pomalidomide. Claims 1-14, 16-19, 20-28 of the '052 patent are directed to

pomalidomide and methods of treatment using pomalidomide, include for oncogenic or cancerous conditions and for reducing TNF- α . Claims 1, 7, and 8 of the '517 patent are directed to methods of treatment using pomalidomide, including for reducing TNF- α . These claims render the Asserted Claims obvious at least because it would have been obvious in view of these claims to use pomalidomide for treatment of multiple myeloma, as claimed by the Zeldis Patents, and the elements of the Asserted Claims are present in or rendered obvious by the prior art as explained above.

Furthermore, each of the '471 patent, '653 patent, '052 patent, and the '517 patent are presently or have previously been listed in the Orange Book for Pomalyst®. In addition, Celgene has represented publicly that the claims of the '471 patent cover treatment of cancer using pomalidomide, and, in particular, the treatment described by the Pomalyst® Label. *See, e.g.*, Celgene Press Releases; *Celgene Corporation v. James E. Rogan and EntreMed, Inc.*, No. 1:02-CV-02277, Dkt. 19-2, ¶¶ 11, 13 (D.D.C. Dec. 23, 2002) (Declaration of Sol J. Barer) (“As a cancer treatment, Celgene’s ACTIMID™ product is protected by U.S. Patent No. 6,316,471.” “The '471 Patent grants Celgene a legal right to exclude others from making, using, or selling ACTIMID™ as a cancer treatment.”); *id.* Dkt. 1, ¶ 6 (Complaint) (“The '471 patent contains a grant to Celgene of the right to exclude others ... from using a method of treating an oncogenic or cancerous condition in a mammal which comprises administering an effective amount of a [pomalidomide].”). *See also* File History of '471 patent, Application For Extension of Patent Term Under 35 U.S.C. § 156 (April 4, 2013) (filed at the PTO for the '471 patent) (“The '471 patent claims, *inter alia*, a method of using the approved product POMALYST®.”). Celgene’s mapping of claims 1, 11, 12, 13, 14, 16, 17, 19 and 20 of the '471 patent to Pomalyst® is

incorporated herein by reference. File History of '471 patent, Application For Extension of Patent Term Under 35 U.S.C. § 156, at 5-9 (April 4, 2013).

2. The Asserted Claims of the Zeldis Patents Are Invalid Over Claims of Celgene's Patents Claiming Lenalidomide

The Asserted Claims of the Zeldis Patents are invalid for ODP over at least claims 1, 2 and 4 of U.S. No. 5,635,517 ("the '517 patent"), claims 18-26 of U.S. Patent No. 6,281,230 ("the '230 patent"), claims 10-17 of U.S. Patent No. 6,555,554 ("the '554 patent"), claims 1-33 of U.S. Patent No. 7,189,740 ("the '740 patent"), claims 1-24 of U.S. Patent No. 7,468,363 ("the '363 patent"), claims 1-15 of U.S. Patent No. 7,968,569 ("the '569 patent"), claims 1-10 of U.S. Patent No. 8,404,717 ("the '717 patent"), claims 1-13 of U.S. Patent No. 8,530,498 ("the '498 patent"), claims 1-25 of U.S. Patent No. 8,648,095 ("the '095 patent"), claims 1-53 of U.S. Patent No. 9,056,120 ("the '120 patent"), claims 1-21 of U.S. Patent No. 9,101,621 ("the '621 patent"), and/or claims 1-25 of U.S. Patent No. 9,101,622 ("the '622 patent"), alone or in combination with one or more of the references listed above.⁵ For example, each of these patents are presently or have previously been listed in the Orange Book for Revlimid®. Further, claims 1, 2 and 4 of the '517 patent are directed to methods of treatment with lenalidomide for reducing TNF- α . Claims 18-26 of the '230 patent are directed to methods of treatment using lenalidomide, including for oncogenic or cancerous conditions. Claims 10-17 of the '554 patent are directed to methods of treatment with lenalidomide for reducing TNF- α . Claims 1-33 of the '740 patent are directed to methods of treatment using lenalidomide, including administering from about 5 to 50 mg of lenalidomide and administering lenalidomide for 21 days followed by 1 week of rest. Claims 1-24 of the '363 patent are directed to methods of treating cancer with

⁵ To the extent the '363 patent, '569 patent, '498 patent, '621 patent and '622 patent expire after the '939 patent and the '428 patent, the claims of the '262 patent are still invalid for ODP as explained in this paragraph.

lenalidomide, including administering 5 to 25 mg per day for 21 days followed by seven days rest in a 28 day cycle. Claims 1-15 of the '569 patent are directed to methods of treating multiple myeloma with lenalidomide, including by administering from 5 to 25 mg per day for 21 days followed by 7 days of rest and the administration of 40 mg of dexamethasone on days 1-4. Claims 1-10 of the '717 patent are directed to methods of treatment with lenalidomide with about 5 to 25 mg/day. Claims 1-13 of the '498 patent are directed to methods of treatment of multiple myeloma with lenalidomide of 25 mg per day for 21 days followed by 7 days of rest and the administration of 40 mg of dexamethasone on days 1-4. Claims 1-25 of the '095 patent are directed to methods of treating multiple myeloma with lenalidomide, including administering from 1 to 50 mg per day for 21 days followed by 7 days of rest and the administration of dexamethasone. Claims 1-53 of the '120 patent are directed to methods of treatment with lenalidomide, including administering from 1 to 25 mg per day for 21 days followed by 7 days of rest and the administration of dexamethasone. Claims 1-21 of the '621 patent are directed to methods of treating multiple myeloma using lenalidomide, including administering from 1 to 50 mg per day (e.g., 2.5 or 5 mg per day) for 21 days followed by 7 days of rest, where the multiple myeloma is relapsed, refractory, or relapsed and refractory, and/or the patient has had previous treatment. Claims 1-25 of the '622 patent are directed to administration of lenalidomide for treatment of multiple myeloma, including administering from 1 to 50 mg per day for 21 days followed by 7 days of rest and the administration of dexamethasone. These claims render the Asserted Claims obvious at least because it would have been obvious to use pomalidomide instead of lenalidomide as claimed for treatment of multiple myeloma. For example, it would have been obvious to administer 1 to 25 mg of pomalidomide daily for 21 days followed by 7 days of rest and with the administration of 40 mg of dexamethasone instead of lenalidomide.

This would have been obvious, for example, in view of the known similarities between the chemical structures of pomalidomide and their mechanisms of action and the knowledge that pomalidomide was more potent than lenalidomide. Thus, for at least these reasons and the reasons described above, the Asserted Claims of the Zeldis Patents are invalid for ODP.

3. Asserted Claims of the '262 Patent Are Invalid Over Claims of the '939 Patent and/or the '428 Patent.

The asserted claims of the '262 patent are invalid for ODP over the asserted claims of the '939 patent and/or the '428 patent, alone or in combination with one or more of the prior art references cited above. For example, as shown in Exhibits B and C, all of the features recited in the claims of the '262 patent are present in the claims of the '939 patent and in the claims of the '428 patent. Additionally, terminal disclaimers were filed during prosecution of both the '939 patent and the '428 patent to overcome ODP rejections of those claims in view the claims 1-29 of the '262 patent. *See* File History of U.S. Patent Appl. No 13/782,612, Terminal Disclaimer & Remarks at 13 (Oct. 9, 2013); File History of U.S. Patent Appl. No 13/782,728, Terminal Disclaimer & Remarks at 14 (Oct. 8, 2013). For at least these reasons, the claims of the '262 patent are rendered obvious and invalid for ODP.

E. Invalidity Under 35 U.S.C. § 112⁶

Under 35 U.S.C. § 112(a), a patent claim is invalid for lack of written description and/or enablement if it does not contain “a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

⁶ The application for the '262 patent was filed August 19, 2008, and therefore pre-AIA 35 U.S.C. 112 (applicable to applications filed before September 16, 2012) applies. The applications for the '929 and '428 were filed on March 1, 2013, and therefore 35 U.S.C. 112 (applicable to applications filed on or after September 16, 2012) applies. As the wording is substantially identical between pre-AIA 35 U.S.C. 112 paragraphs 1 and 2, and 35 U.S.C. 112(a) and (b) respectively, citations to § 112 in this section are to 35 U.S.C. 112.

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.” 35 U.S.C. § 112(a). The claims may be no broader than the supporting disclosure, particularly where the patentee has indicated that a certain feature is an essential element of the invention. *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1478-79 (Fed. Cir. 1998).

Further, “[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.” 35 U.S.C. § 112(b). Accordingly, “a patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.” *Nautilus, Inc. v. Biosig. Instruments, Inc.*, 134 S. Ct. 2120 (2014).

1. Invalidity Under 35 U.S.C. § 112 for Indefiniteness

Defendants contend that the following claim limitations of the Zeldis Patents render the claims that include them, and all claims that depend from such claims, invalid:

- “which patient has received previous therapy for multiple myeloma” (’939 claims 1–14, 16–35; ’428 claims 1–27), “wherein the patient has received previous therapy” (’262 claims 6–9)
- “relapsed, refractory, or relapsed and refractory,” “relapsed and refractory,” “relapsed,” “refractory” (’262 claims 2, 4, 5, 29; ’939 claims 1–14, 16–25; ’428 claims 1–21)
- “disease progression” (’262 claims 7 and 8; ’939 claims 2, 5, 20, 26–35; ’428 claims 2, 5, 16, 22–27)
- “administering a therapeutically effective amount of an additional active agent,” “wherein the additional active agent is dexamethasone,” “wherein 40 mg dexamethasone is administered,” “administering [] 40 mg of dexamethasone,” “wherein the dexamethasone is orally administered once daily on days 1, 8, 15 and 22 of each 28 day cycle” and “wherein the dexamethasone is orally administered once a week of each 28

day cycle” (’262 claims 1, 2, 4–16, 18–27, 29; ’939 claims 21–25, 33–35; ’428 claims 17–21, 27)

- “one or more cycles, each of which comprises administering the compound for a period of time followed by a period of rest” (’939 claims 1–14, 16–35)
- “[]mg per day of a compound having the formula [] or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof,” “[] mg per day of a compound having the formula [] or a solvate thereof” (’262 claims 1, 2, 4–16, 18–19; ’939 claims 1–11, 13, 14, 16–28, 30–35; ’428 claims 1–27)

a. “which patient has received previous therapy for multiple myeloma” (’939 claims 1–14, 16–35; ’428 claims 1–27), “wherein the patient has received previous therapy” (’262 claims 6–9)

Claims 1 and 22 of the ’428 patent, and claims 1 and 26 of the ’939 patent, recite a method of treating multiple myeloma, for “which patient has received previous therapy for multiple myeloma.” Claim 6 of the ’262 patent recites “wherein the patient has received previous therapy,” from which claims 7 to 9 depend.

These terms render these claims indefinite because a POSA would not know with reasonable certainty what constitutes “previous therapy,” such as whether “previous therapy” could include more than one treatment. Neither the specification nor the file history inform a POSA as to the meaning of this term or reasonably define the methods of treatment falling within the scope of the claims.

For example, the specification does not define “previous therapy.” The importance of the patient’s prior therapy is emphasized in the specification of the Zeldis Patents, which states there is a “significant need” for methods of treating “diseases that are refractory to standard treatments.” (’262 patent at 3:8-14). The specification also states that:

This invention encompasses methods of treating patients who have been previously treated for cancer or diseases or disorders associated with, or characterized by, undesired angiogenesis, but are non-responsive to standard therapies, as well as those who have not previously been treated.

(’262 patent at 17:52-56.) However, this does not explain what constitutes a “previous therapy.” For example, it is unclear whether a “previous therapy” includes one or more treatments, and, if more than one, whether those previous treatments must be concurrent. The claims further do not specify what condition the “previous therapy” is with respect to. The POSA would not have been able to determine with reasonable certainty whether a particular therapy falls within the claims, and thus infringes, or falls outside of the claims, and thus does not infringe. Additionally, for example, claim 3 of the ’939 patent depends from claim 1 and recites “wherein the previous therapy is treatment with thalidomide, a proteasome inhibitor, or a combination thereof.” It is unclear, for example, whether “previous therapy” with “a combination thereof” refers to a single treatment with both drugs concurrently, or to multiple treatments with each drug sequentially.

Accordingly, these terms do not allow a POSA to determine with reasonable specificity the metes and bounds of the claims, and thus these claims of the Zeldis Patents, and all claims that depend from them, are indefinite.

b. “relapsed, refractory, or relapsed and refractory,” “relapsed and refractory,” “relapsed,” “refractory” (’262 claims 2, 4, 5, 29; ’939 claims 1–14, 16–25; ’428 claims 1–21)

Claim 1 of the ’428 patent and claim 1 of the ’939 patent each recite a method of treating multiple myeloma, “wherein the multiple myeloma is relapsed, refractory, or relapsed and refractory multiple myeloma.” Claims 2, 4 and 5 of the ’262 patent recite a method of treating multiple myeloma, wherein the multiple myeloma is “relapsed and refractory,” “relapsed,” and “refractory,” respectively. Claim 29 of the ’262 patent also recites a method of treating multiple myeloma, wherein the multiple myeloma is “relapsed and refractory.”

These terms render these claims indefinite because a POSA would not know with reasonable certainty whether a patient receiving treatment for multiple myeloma has “relapsed,”

“refractory,” or “relapsed and refractory” multiple myeloma. Neither the specification nor the file history make clear to a POSA what disease state of the patient is required in order for the patient to fall under one or more of these descriptions.

For example, the specification refers to treatment of patients “with relapsed/refractory multiple myeloma” and states:

Patients were at least 18 years old, had been diagnosed with multiple myeloma (with paraprotein in serum and/or urine), and were considered refractory to treatment after at least two cycles of treatment, or have relapsed after two cycles of treatment.

Patients who have progressive disease, according to the Southwest Oncology Group (SWOG) criteria, on their prior regimen are considered treatment refractory. Relapse following remission is defined as >25% increase in M component from baseline levels; reappearance of the M paraprotein that had previously disappeared; or a definite increase in the size and number of lytic bone lesions recognized on radiographs.

(’262 patent at 33:6-17.) The specification also states:

Patients with relapsed and refractory Dune-Salmon stage III multiple myeloma, who have either failed at least three previous regimens or presented with poor performance status, neutropenia or thrombocytopenia, are treated with up to four cycles of combination of melphalan (50 mg intravenously), an immunomodulatory compound of the invention (about 1 to 150 mg orally daily), and dexamethasone (40 mg/day orally on days 1 to 4) every four to six weeks.

(’262 patent at 37:59-66.) The specification and file history do not define the terms “refractory,” “relapsed” or “refractory and relapsed” multiple myeloma. It is therefore unclear at least as to what constitutes each of “refractory,” “relapsed,” or “refractory and relapsed” multiple myeloma. For example, it is unclear whether a patient that is considered “refractory and relapsed” must separately meet both definitions of “refractory” and “relapsed” multiple myeloma, and what each of those definitions would require. Thus, the POSA would not have been able to determine with reasonable certainty whether a particular treatment falls within the claims, and thus infringes, or falls outside of the claims, and thus does not infringe.

Accordingly, these terms do not allow a POSA to determine with reasonable specificity the metes and bounds of the claims, and thus these claims of the Zeldis Patents, and all claims that depend from them, are indefinite.

c. “disease progression” (’262 claims 7 and 8; ’939 claims 2, 5, 20, 26–35; ’428 claims 2, 5, 16, 22–27)

Claim 2 and 22 of the ’428 recite methods of treating multiple myeloma wherein the patient “has demonstrated disease progression on the previous therapy.” Claim 5 of the ’428 patent depends from claim 2. Claim 16 of the ’428 patent depends from claim 1 and recites that the compound is administered “until disease progression.” Claims 7 and 8 of the 262 patent recite methods of treating multiple myeloma wherein the patient “has demonstrated disease progression on previous therapy.” Claims 2 and 26 of the ’939 patent recite methods of treating multiple myeloma “wherein the patient has demonstrated disease progression on the previous therapy.” Claim 20 of the ’939 patent recites administration “until disease progression.”

The term “disease progression” renders these claims indefinite because, for example, a POSA would not know with reasonable certainty whether a patient being treated for multiple myeloma has shown disease progression, how disease progression is measured or determined, how much disease progression is required to infringe the claims, and any difference between disease progression and relapsed or refractory multiple myeloma. Neither the specification nor the file history make clear to a POSA whether a given method of treating multiple myeloma falls within the scope of these claims.

For example, in Example 6.5.2 “Treatment of Relapsed Multiple Myeloma,” the specification refers to patients who “did not exhibit disease progression.” In Example 6.5.6 “Treatment of Relapsed or Refractory Multiple Myeloma,” the specification refers to treatment “continued until the disease progression.” However, the specification fails to define what

disease state or physical condition is required to constitute “disease progression.” There are numerous methods of determining the disease state of patients with multiple myeloma and varying severity of signs or symptoms of the disease. The specification fails to inform a POSA how “disease progression” should be assessed in order to determine whether a method of treatment falls within the scope of the claims.

Accordingly, this term does not allow a POSA to determine with reasonable specificity the metes and bounds of the claims, and thus these claims of the Zeldis Patents, and all claims that depend from them, are indefinite.

- d. “administering a therapeutically effective amount of an additional active agent,” “wherein the additional active agent is dexamethasone,” “wherein 40 mg dexamethasone is administered,” “administering [] 40 mg of dexamethasone,” “wherein the dexamethasone is orally administered once daily on days 1, 8, 15 and 22 of each 28 day cycle” and “wherein the dexamethasone is orally administered once a week of each 28 day cycle” (’262 claims 1, 2, 4–16, 18–27, 29; ’939 claims 21–25, 33–35; ’428 claims 17–21, 27)**

Claim 17 of the ’428 patent depends from claim 1 and further comprises “administering a therapeutically effective amount of an additional active agent.” Claim 18 of the ’428 patent depends from claim 17 and recites “wherein the additional active agent is dexamethasone.” Claim 21 of the ’939 patent recites the method of claim 1 which further comprises “administering a therapeutically effective amount of an additional active agent.” Claim 22 of the ’939 patent depends on claim 1 and recites “wherein the additional active agent is dexamethasone.” Claim 33 of the ’939 patent recites the method of claim 26 which further comprises “administering a therapeutically effective amount of dexamethasone.”

These terms render these claims indefinite. For example, the POSA would not have been able to determine with reasonable certainty whether a particular administration of dexamethasone or additional active agent fell within the scope of the claims, and thus infringed,

or fell outside of the claims, and thus did not infringe. The Zeldis Patents disclose many active agents and provide no guidance as to how such drugs may be safely administered. For example, the specification lists approximately 600 compounds as “other pharmacologically active compounds (“second active agents”).” (“5.2 Second Active Agents,” ’262 at 11:47-16:7.) The specification states:

In one embodiment, an immunomodulatory compound of the invention can be administered in an amount of from about 0.1 to about 150 mg, and preferably from about 1 to about 25 mg, more preferably from about 2 to about 10 mg orally and daily alone, or in combination with a second active agent disclosed herein (see, e.g., section 5.2), prior to, during, or after the use of conventional therapy.

(’262 patent at 22:51–57.) The specification also states:

the specific amount of the anti-cancer drug will depend on the specific agent used, the type of cancer being treated or managed, and the amount(s) of an immunomodulatory compound of the invention and any optional additional active agents concurrently administered to the patient.

(’262 patent at 18:63–19:2.) The specification provides no guidance to a POSA as to the amount of each of these additional active agents to administer to a patient, the frequency and/or route of administration required in order to “administer a therapeutically effective amount.”

Claim 19 of the ’428 patent depends from claim 18 and recites “wherein 40 mg dexamethasone is administered.” Claims 1 and 20 of the ’262 patent recite a method of treating multiple myeloma which comprises “administering 40 mg of dexamethasone.” Claim 23 of the ’939 patent recites the method of claim 22 “wherein 40 mg dexamethasone is administered.” Claim 34 of the ’939 patent recites the method of claim 33 “wherein 40 mg dexamethasone is administered.” These terms render the claims indefinite because a POSA would not know with reasonable certainty whether a given dosage regimen would fall within the scope of the claims, at least because the terms could be understood to refer to administration of 40 mg dexamethasone on the same daily schedule as the compound of claim 1, or a single administration of 40 mg

dexamethasone. Neither the specification nor the file history inform a POSA as to the time of administration relative to the administration of 3A-thalidomide (i.e. concurrent or sequential, or separated by days), the dose frequency, or the route of administration of 40 mg dexamethasone. For example, the specification refers to “Treatment of Relapsed or Refractory Multiple Myeloma” in Example 6.5.6 and states:

Patients with relapsed and refractory Dune-Salmon stage III multiple myeloma, who have either failed at least three previous regimens or presented with poor performance status, neutropenia or thrombocytopenia, are treated with up to four cycles of combination of melphalan (50 mg intravenously), an immunomodulatory compound of the invention (about 1 to 150 mg orally daily), and dexamethasone (40 mg/day orally on days 1 to 4) every four to six weeks. Maintenance treatment consisting of daily an immunomodulatory compound of the invention and monthly dexamethasone are continued until the disease progression.

(’262 patent at 37:59-38:2 (emphasis added).) The administration schedule of the “compound of the invention” in Example 6.5.6 does not align to the schedule in the claims. The specification provides no other disclosure of administration of 40 mg dexamethasone. It is therefore unclear whether the dexamethasone is required to be administered on the same schedule as 3A-thalidomide, or a different schedule, whether such administrations are concurrent or sequential, and the appropriate route of administration to meet the “therapeutically effective” limitation.

Claim 20 of the ’428 patent depends from claim 18 and recites “wherein the dexamethasone is orally administered once daily on days 1, 8, 15 and 22 of each 28 day cycle.” ’428 patent at 13-15. Claim 21 of the ’428 patent depends from claim 18 and recites “wherein the dexamethasone is orally administered once a week of each 28 day cycle.” ’428 patent at 40:16-17. Claims 14 and 15 of the ’262 patent recite the method of claim 1 “wherein the dexamethasone is orally administered [] once daily on days 1, 8, 15 and 22 of each 28 day cycle,” and “wherein the dexamethasone is orally administered in an amount of about 40 mg once a week of each 28 day cycle,” respectively. ’428 patent at 39:48-40:15. Claim 25 of the

'262 patent recites the method of claim 20 "wherein the dexamethasone is administered once daily on days 1, 8, 15 and 22 in a 28 day cycle." '428 patent at 40:41-42.

These terms render these claims indefinite because at least, for example, a POSA would not know with reasonable certainty whether these doses are to be administered concurrently or sequentially with 3A-thalidomide, or on a completely different schedule. Neither the specification nor the file history make clear to a POSA whether a given dosing regimen falls within the scope of these claims.

Because it is insufficient "that a court can ascribe some meaning to a patent's claims," this ambiguity renders the claims indefinite. *Nautilus*, 134 S. Ct. at 2130. Accordingly, these terms do not allow a POSA to determine with reasonable specificity the metes and bounds of the claims, and thus these claims of the Zeldis Patents, and all claims that depend from them, are indefinite.

e. "one or more cycles, each of which comprises administering the compound for a period of time followed by a period of rest" ('939 claims 1-14, 16-35)

Claims 1 and 26 of the '939 patent recite a method of treating multiple myeloma "wherein the compound is administered in one or more cycles, each of which comprises administering the compound for a period of time followed by a period of rest." '939 patent at 38:65-39:20; '939 patent at 40:15-34.

This term renders these claims indefinite because, for example, a POSA would not know with reasonable certainty what a cycle comprises, the length of time of a cycle or of a period of time or of a period of rest, the length of time between "administering the compound" and "rest," or the length of time after the "rest" until the next cycle begins. Neither the specification nor the file history make clear to a POSA whether a given dosage regimen falls within the scope of these claims, as these terms are undefined. Further, "one or more" does not limit the "cycles" or

provide a POSA with any certainty as to how many cycles to utilize in order to practice the method of those claims.

Accordingly, this term does not allow a POSA to determine with reasonable specificity the metes and bounds of the claims, and thus these claims of the Zeldis Patents, and all claims that depend from them, are indefinite.

- f. **“[]mg per day of a compound having the formula [] or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof,” “[] mg per day of a compound having the formula [] or a solvate thereof”** (**'262 claims 1, 2, 4–16, 18–19; '939 claims 1–11, 13, 14, 16–28, 30–35; '428 claims 1–27**)

Claim 1 of the '428 patent recites a method of treating multiple myeloma comprising “administering from about 1 mg to about 5 mg per day of a compound [] or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.” '428 patent at 39:2-22. Claim 22 of the '428 patent recites a method of treating multiple myeloma comprising “administering [] from about 1 mg to about 5 mg per day of a compound [] or a solvate thereof.” '428 patent at 40:18-35. Claim 1 of the '262 patent recites a method of treating multiple myeloma comprising “administering [] from about 1 mg to about 5 mg per day of a compound [] or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.” '262 patent at 38:17-34. Claim 1 of the '939 patent recites a method of treating multiple myeloma comprising “administering [] from about 1 mg to about 5 mg per day of a compound [] or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.” '939 patent at 38:65. Claim 26 of the '939 patent recites a method of treating multiple myeloma comprising “administering [] from about 1 mg to about 5 mg per day of a compound [] or a solvate thereof.” '939 patent at 40:15-34.

These terms render these claims indefinite because, for example, a POSA would not know with reasonable certainty whether the dosage of the 3A-thalidomide is calculated using the weight of the freebase, or using the weight of the salt or solvate. Neither the specification nor

the file history make clear to a POSA whether a given dosage regimen falls within the scope of these claims. Whether or not these claims are infringed depends on the method used to measure the weight, and a method of treatment could infringe under one method of weighing and not under another.

For example, the specification states:

Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. However, typical dosage forms of the invention comprise an immunomodulatory compound of the invention or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof in an amount of from about 0.10 to about 150 mg.

'262 patent at 26:48-56. Because it is insufficient "that a court can ascribe some meaning to a patent's claims," this ambiguity renders the claims indefinite. *Nautilus*, 134 S. Ct. at 2130.

Accordingly, these terms do not allow a POSA to determine with reasonable specificity the metes and bounds of the claims, and thus these claims of the Zeldis Patents, and all claims that depend from them, are indefinite.

2. **Invalidity Under 35 U.S.C. § 112 for Lack of Written Description and/or Enablement**

The specification must "contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same" to meet the requirements of 35 U.S.C. § 112. The Asserted Claims of the Zeldis Patents are invalid for lack of written description because the claimed subject matter is not adequately described by their disclosure, and because the specification fails to enable the full scope of the claims.

The test for written description "requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art. Based on that inquiry,

the specification must . . . show that the inventor actually invented the invention claimed.” *Ariad Pharms., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*). It is well settled that the “full scope of the claimed invention must be enabled.” *Sitrick v. Dreamworks, LLC*, 516 F.3d 993, 999 (Fed. Cir. 2008); *see also Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371, 1379 (Fed. Cir. 2007). Claims are enabled when they may be practiced without undue experimentation. *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 940 (Fed. Cir. 2010). The factors to be considered in determining whether a disclosure would require undue experimentation include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

The Zeldis Patents’ specifications provide a vague general description of treating multiple myeloma. An invitation for carrying out clinical research in 2003 is not sufficient written description or enablement of the specific methods and subject matter added during prosecution of the applications that led to the Zeldis Patents, which were filed in 2008 and later. *Ariad*, 598 F.3d at 1351 (a description that amounts “to no more than a ‘wish’ or ‘plan’ for obtaining [the claimed invention]” fails the written description requirement).

In order to gain allowance of the Asserted Claims over the prior art, the Applicant included specific limitations on the administration of the 3A-thalidomide and on the patient population being treated. Applicant argued that the dosing regimens and patient populations added to the claims were non-obvious. For example, during the prosecution of the ’262 patent,

the Applicant held an interview with PTO Examiner on March 6, 2012 where the claim rejections over the prior art were discussed. The summary of the interview states:

Discussed potential allowability of claims if independent claims are amended to incorporate the limitations of claim 1 of U.S. Pat 7,968,569. Particularly the cyclical administration of the current amounts of the compound for 21 consecutive days followed by 7 consecutive days of rest from administration of the compound in a 28 day cycle in combination with 40 mg of dexamethasone.

File History of U.S. App. No. 12/229,074, Interview Summary, March 6, 2012. Subsequently, claims were added to the application reciting cyclical administration with specific amounts of the compound (*e.g.* from “about 1 mg to about 4 mg per day;” “about 1 mg per day;” “about 2 mg per day;” “about 3 mg per day;” “about 4 mg per day,” U.S. App. No. 12/229,074, Supplemental Response and Amendment, March 15, 2012 at 1–5; Examiner Amendment and Allowance, April 9, 2012 at 2). In the applications that ultimately issued as the ’939 and ’428 patents, the Applicant limited the claimed subject matter to treating relapsed and/or refractory multiple myeloma and argued that successfully treating such patients by the claimed method was unexpected at the time of the invention.⁷

A POSA reading the four corners of the specification common to the Zeldis Patents would not understand that named inventor Dr. Zeldis had invented the methods that the attorneys prosecuting his application later claimed. As the Federal Circuit has stated, the purpose of the written description requirement is to “ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor’s contribution to the field of art as described in the patent specification. It is part of the *quid pro quo* of the patent grant and ensures that the public receives a meaningful disclosure in exchange for being excluded from practicing

⁷ See, *e.g.* U.S. App. No. 13/782,728, Office Action and Interview Summary, July 8, 2013 at 2, and Amendment and Response, October 8, 2013 at 7; U.S. App. No. 13/78,2612, Office Action and Interview Summary, July 9, 2013 at 2, and Amendment and Response, October 8, 2013 at 6, 12 and 13.

an invention for a period of time.” *Ariad Pharm., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1354 (Fed. Cir. 2010) (internal citations removed). The Asserted Claims of the Zeldis Patents were drafted with hindsight knowledge of research done by others years after the specification was filed. *See e.g.* Richardson 2013. Dr. Zeldis could not have enabled and described methods that he did not know of or invent and the Zeldis Patents fail to describe, identify, or teach effective methods of treating multiple myeloma through administration of 3A-thalidomide.

Certain claims of the Zeldis Patents⁸ recite a method of treating multiple myeloma, comprising administering either “a compound [...] or a pharmaceutically acceptable salt, solvate or stereoisomer thereof,” or “a compound [...] or a solvate thereof.” The specification does not provide adequate written description support for the full scope of the claimed methods and fails to enable a POSA to practice the full scope of the claimed methods. With respect to “stereoisomers,” the specification provides no guidance to a POSA as to the doses of single enantiomers in the claimed method of treating multiple myeloma. The doses disclosed in the specification for Actimid relate to racemic mixtures and there is no disclosure or working example of a dose for a single enantiomer. *See, e.g.,* Teo *et al.*, “*Chiral inversion of the second generation IMiD™ CC-4047 (Actimid™) in human plasma and phosphate-buffered saline,*” *Chirality*, 2003, 15:348-351. Even though a POSA would find it obvious to use single enantiomers to treat multiple myeloma according to the claimed methods, the POSA would not have understood from the disclosures in the specification common to the Zeldis Patents that Dr. Zeldis possessed as his invention methods of treating multiple myeloma using single enantiomers of the claimed compound, yet the claims are broad enough to include single enantiomers.

With respect to “salts,” the specification states, for example:

⁸ ’262 claims 1, 2, 4–16, 18–27, 29; ’939 claims 1–11, 13, 14, 16–28, 30–35; ’428 claims 1–27.

the term “pharmaceutically acceptable salt” encompasses non-toxic acid and base addition salts of the compound to which the term refers. Acceptable non-toxic acid addition salts include those derived from organic and inorganic acids or bases known in the art, which include, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulphonic acid, acetic acid, tartaric acid, lactic acid, succinic acid, citric acid, malic acid, maleic acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, embolic acid, enanthic acid, and the like.

’262 patent at 9:57-67. The specification also states:

Compounds that are acidic in nature are capable of forming salts with various pharmaceutically acceptable bases. The bases that can be used to prepare pharmaceutically acceptable base addition salts of such acidic compounds are those that form non-toxic base addition salts, i.e., salts containing pharmacologically acceptable cations such as, but not limited to, alkali metal or alkaline earth metal salts and the calcium, magnesium, sodium or potassium salts in particular. Suitable organic bases include, but are not limited to, N-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), lysine, and procaine.

’262 patent at 10:1–12.

The claims therefore encompass an incredibly broad number of possible salt forms, and the specification fails to inform a POSA of the important physicochemical properties required and whether specific salts impact on the therapeutic effectiveness of the 3A-thalidomide in the context of the claimed methods. The Zeldis Patents also contain no working examples of any salt form of 3A-thalidomide. The POSA would not have understood from these disclosures that Dr. Zeldis possessed as his invention methods of treating multiple myeloma using all of these possible salt forms, yet the claims do not limit the salt form included within the scope of the claims. Similarly, there is also no specific description of “solvates” of 3A-thalidomide and a POSA would not understand from specification that Dr. Zeldis was in possession of any solvates that could be used in the claimed invention. *Boston Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1364 (Fed. Cir. 2011) (“the lack of any disclosure of examples may be considered when determining whether the claimed invention is adequately described”). For at least these reasons, the Zeldis Patents do not provide adequate written description support for a POSA to reasonably

conclude that Dr. Zeldis had developed and was in possession of a method of treating multiple myeloma comprising administration of a “pharmaceutically acceptable salt, solvate or stereoisomer” of the claimed compound. Further, the Zeldis Patents do not enable a POSA to make and use such compounds for the treatment of multiple myeloma without undue experimentation.

The Asserted Claims of the Zeldis Patents recite a method of treating multiple myeloma, comprising administering “about 1 mg to about 5 mg per day” of 3A-thalidomide, or “about 4 mg,” “about 3 mg,” “about 2 mg,” or “about 1 mg.” Although these doses would have been obvious in view of the prior art, all of the Asserted Claims are also invalid because the specification of the Zeldis Patents does not provide adequate written description support for treatment of multiple myeloma with these claimed doses. As explained elsewhere in these contentions, the prior art had already taught the use of 3A-thalidomide for the treatment of multiple myeloma by oral dosing. To the extent anything is critical, novel or non-obvious about the specific claimed dose amounts and dosing schedule (Defendants contend there is none) the Zeldis Patents do not describe it. *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1326–27 (Fed. Cir. 2000) (“one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say here is my invention. In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure.”) The specification of the Zeldis Patents lacks description of the appropriate dose of 3A-thalidomide for treating multiple myeloma. For example, the specification is devoid of any data, studies, or other evidence Dr. Zeldis had actually invented a method of treatment of multiple myeloma by administering 3A-thalidomide in the claimed amounts. The only example of 3A-thalidomide in patients described in the Zeldis Patents is not indicative of efficacy of

treatment, nor is it clear whether the data is prophetic or real. Thus, the specification does not inform a POSA as to whether the recited doses would be effective in treating multiple myeloma. The POSA would not have understood from these disclosures that Dr. Zeldis possessed as his invention methods of treating multiple myeloma using the recited dosages as claimed. For at least these reasons, the Zeldis Patents do not provide adequate written description support for a POSA to reasonably conclude that Dr. Zeldis had developed and was in possession of a method of treating multiple myeloma, comprising administering “from about 1 mg to about 5 mg per day of a compound,” or “about 4 mg,” “about 3 mg,” “about 2 mg,” or “about 1 mg.”

Additionally, certain claims of the Zeldis Patents require administering to a patient that has “received previous therapy.” Certain dependent claims⁹ recite “wherein the previous therapy is treatment with thalidomide, a proteasome inhibitor, or a combination thereof;” “wherein the previous therapy is treatment with a proteasome inhibitor;” “wherein the previous therapy is treatment with a proteasome inhibitor.” Certain claims of the Zeldis Patents require the patient have refractory multiple myeloma, relapsed multiple myeloma, or relapsed and refractory multiple myeloma, or “disease progression.” These claims are invalid because the specification of the Zeldis Patents does not provide adequate written description support for the full scope of the claimed methods of treating multiple myeloma in patients with these claimed conditions. For example, the specification lacks description of the dose of 3A-thalidomide for treating each these conditions. For example, the specification has no examples of treating patients having any of these conditions with any of the claimed dosages. The specification does not inform a POSA as to whether the recited doses would be effective. As stated above, the specification does not identify any actual clinical studies or provide any data showing treatment of multiple myeloma

⁹ '939 patent claims 3, 5 and 27; '262 patent claim 9; '428 patent claims, 3, 5, 23.

patients with any of these conditions. Moreover, the specification lists proteasome inhibitors as one of approximately 600 anti-cancer drugs, and does not describe treating patients with 3A-thalidomide who have been previously treated with any of these proteasome inhibitors. '262 patent at 15:25. The POSA would not have understood from these disclosures that the named inventor possessed as his invention methods of treating multiple myeloma in patients with these conditions using the recited dosages as claimed. For instance, the POSA would not have understood from these disclosures that the named inventor possessed as his invention methods of treating multiple myeloma for patients that have received all of the possible previous therapies falling within these claims. For at least these reasons, the Zeldis Patents do not provide adequate written description support for a POSA to reasonably conclude that the Dr. Zeldis had developed and was in possession of a method of treating multiple myeloma comprising administration of specific amounts or specific ranges of 3A-thalidomide for refractory multiple myeloma, or for relapsed multiple myeloma, or for relapsed and refractory multiple myeloma, or for patients that have received any previous therapy, or for patients demonstrating "disease progression."

The specification also has no examples of treating patients with multiple myeloma using the claimed dosing schedules. As stated above, the specification does not identify any actual clinical studies or provide any data showing treating of multiple myeloma patients with any of the claimed dosing schedules. The only example of 3A-thalidomide in patients described in the Zeldis Patents recites administering daily doses for 28 days. This example is not indicative of therapeutic efficacy, nor does the example include multiple cycles or any rest days or periods. The POSA would not have understood from these disclosures that the named inventor possessed as his invention methods of treating multiple myeloma in patients with these conditions using the recited dosages as claimed. For example, the specification does not inform a POSA as to

whether the recited dosing schedules would be effective. Furthermore, claims 1–14, 16–35 of the '939 patent claim “one or more cycles, each of which comprises administering the compound for a period of time followed by a period of rest,” which could broadly include any number of cycles with a period of time for rest. '939 patent at 38:65-39:47; '939 patent at 39:50-40:57. The POSA would not have understood Dr. Zeldis to have possessed as his invention administering 3A-thalidomide with any possible schedule, nor is such breadth of schedules enabled by the specification. For at least these reasons, the Zeldis Patents do not provide adequate written description support for a POSA to reasonably conclude that the Dr. Zeldis had developed and was in possession of a method of treating multiple myeloma comprising administration according to the claimed schedules.

Further, to the extent Celgene argues that the claimed dosages and/or dose schedules, or that treatment of multiple myeloma in patients with any of the above conditions and/or previous therapies, are non-obvious, the Asserted Claims are not enabled. For example, for at least the reasons provided above, the specification does not enable the POSA to use the dose amounts and/or dosing schedules to treat multiple myeloma according to the claimed methods without undue experimentation. The Zeldis Patents do not provide any data, clinical or otherwise, regarding actual administration of 3A-thalidomide to patients. The only example in the Zeldis Patents concerning 3A-thalidomide in patients is a Phase I pharmacokinetic study, which does not assess the efficacy of the proposed treatment. *Acorda Therapeutics Inc. v. Apotex Inc.*, CIV.A. 07-4937 GEB-M, 2011 WL 4074116, at *25 (D.N.J. Sept. 6, 2011), *aff'd*, 476 Fed. Appx. 746 (Fed. Cir. 2012) (finding undue experimentation would be necessary to practice the claimed invention to its full scope, including “substantial, iterative testing involving experiments such as those prepared for the NDA or the ANDA with large enough sample sizes to be

considered legitimate”). This Phase I study was designed and conducted by people other than Dr. Zeldis. *See, e.g.* Schey I, Schey II, Schey III; Richardson 2013. Further, this example does not administer doses according to the claimed dosing schedules or patients having all of the recited previous therapies. The prior art disclosures described in these contentions are similar to those in the Zeldis Patent, such that if the Zeldis Patents’ specifications enable the claims, then the prior art disclosures are sufficient to render the Asserted Claims obvious. Accordingly, the Asserted Claims of the Zeldis Patent are invalid because the specification does not enable the full scope of the claims.

Several other claim elements of the Asserted Claims of the Zeldis Patents are simply obvious variations of what was in the prior art. These elements are nonetheless not described in the Zeldis Patents to show a POSA that Dr. Zeldis was in possession of methods of treating multiple myeloma that are specifically recited in the claims. As such, claims that recite the following elements are invalid: “wherein the patient is 65 years or younger” and “wherein the patient is older than 65 years;”¹⁰ “which further comprises administering a therapeutically effective amount of an additional active agent” and “therapeutically effective amount.”¹¹

Regarding claims that recite a patient “65 years or younger” and “older than 65 years,” the Zeldis Patents provide no examples of treatment in patients stated to be older or younger than 65. For example, the specification states that the “[i]nvention also encompasses methods of treating patients regardless of patient’s age, although some diseases or disorders are more common in certain age groups.” ’262 patent at 17:56–59. A POSA reading this statement in the specification, and finding no other disclosure in relation to patient age, would not reasonably

¹⁰ ’939 patent claims 6 and 7; ’428 patent claims 6 and 7.

¹¹ ’939 claims 21, 22, 24, 25, 33, 35; ’428 claims 17, 18, 20, 21, 27.

conclude that Dr. Zeldis had developed and was in possession of a method of treating multiple myeloma in patients of a certain age. Further, the Zeldis Patents do not enable a POSA to determine how to treat multiple myeloma in the recited age groups without undue experimentation. For example, the '428 patent does not inform a POSA as to whether modifications to the claimed dosage regimens are necessary as a result of the patient's age, and if so, what those appropriate modifications are.

Regarding claims that recite a "therapeutically effective" dosage of an additional active agent or dexamethasone, to the extent that Celgene argues these claims are non-obvious, a POSA would not know with reasonable certainty whether any given dose is therapeutically effective. Neither the specification nor the file history make clear to a POSA the method by which therapeutic effectiveness is to be determined. Additionally, neither the specification nor the file history inform the POSA as to how much of an additional active agent or dexamethasone to administer, the frequency of administration, the route of administration, and whether the administration is concurrent or sequential with the administration of the compound of the claims. The specification does not define a "therapeutically effective amount" of any compound, let alone of an additional active agent or dexamethasone. For example, the specification describes administering "the immunomodulatory compound ... in combination with another drug ('second active agent')." Yet, the specification identifies approximately 600 compounds as possible "second active agents." The specification does not inform a POSA as to which particular additional active agent(s) would be effective in the method of the claims, how a POSA should select such an agent, or how a therapeutically effective amount is to be determined for each of these active agents. For example, with regard to dosing, the specification states that:

The specific amount of the second active agent will depend on the specific agent used, the type of disease being treated or managed, the severity and stage of

disease, and the amount(s) of immunomodulatory compounds of the invention and any optional additional active agents concurrently administered to the patient.

'262 at 18:63-19:2.

The specification does not inform a POSA as to how each of these factors impacts on the dose of an “additional active agent” or inform a POSA how the dosage, frequency of doses, and route of administration should be determined. For example, the specification does not explain how much of the additional active agent or dexamethasone to administer, the frequency of administration, the route of administration, and whether the administration is concurrent or sequential with the administration of 3A-thalidomide. There are no examples in the specification of methods of treating multiple myeloma with 3A-thalidomide as claimed in combination with an additional active agent. Nor does the specification have any clinical data. A POSA would not have understood from these disclosures that the named inventor possessed as his invention methods of treating multiple myeloma with 3A-thalidomide as claimed in combination with all of the possible additional active agents and all the possible dosing regimens falling within the scope of these claims. Further, the specification does not enable a POSA to treat patients with 3A-thalidomide as claimed in combination with all of the possible additional active agents without undue experimentation. Therefore, the full scope is not sufficiently described or enabled by the Zeldis Patents.

Additionally, to the extent that Celgene argues that the claimed formulations of the '427 patent are non-obvious, claims of the Zeldis Patents to pomalidomide dosage forms (e.g., “wherein the capsule comprises the compound, mannitol and pre-gelatinized starch”)¹² lack written description support and are not enabled. For example, the specification of the Zeldis Patents states:

¹² '262 patent claims 19 and 27; '428 patent claim 14; '939 patent claim 16.

Lactose-free compositions of the invention can comprise excipients that are well known in the art and are listed, for example, in the U.S. Pharmacopeia (USP) 25-NF20 (2002). In general, lactose-free compositions comprise active ingredients, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. ('428 patent at 2:15–23)

Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include [] mannitol, [] pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form. ('428 patent at 28:18–26)

The specification of the Zeldis Patents provides no examples of dosage forms for treatment of multiple myeloma, dosage forms including pomalidomide, or dosage forms including the recited excipients. A POSA would not have understood that the named inventor was in possession of an invention including specific combinations of excipients with pomalidomide in a capsule dosage form and that were suitable for “treating multiple myeloma.” Additionally, a POSA would have had to undertake undue experimentation in order to arrive at pomalidomide dosage forms suitable for “treating multiple myeloma” and containing the recited excipients. *See, e.g.*, Tutino Declaration filed during prosecution of the '427 patent application.

For at least these reasons, the Zeldis Patents do not provide adequate written description support for a POSA to reasonably conclude that the inventors had developed and were in possession of a method of treating multiple myeloma as described in the Asserted Claims. Further, the Zeldis Patents do not enable a POSA to practice the full scope of the Asserted Claims without undue experimentation.

F. Invalidity Under 35 U.S.C. §§ 101 and 112 for Lack of Utility/Enablement

A claimed invention must have “a specific and substantial utility to satisfy § 101.” *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005). Section 101 requires that any patentable invention be useful and, accordingly, that the subject matter of the claim be operable. “Inventions do not meet the utility requirement if they are objects upon which scientific research could be

performed with no assurance that anything useful will be discovered in the end.” *In re '318 Patent Litigation*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) (internal citations omitted). The specification must demonstrate that the “invention is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research.” *Id.* In addition, the specification “must disclose a use which is not so vague as to be meaningless.” *Id.* Moreover, the utility of a claimed invention must be substantial, specifically where an alleged new process provides a chemical compound that was already in the public domain. *Brenner v. Manson*, 383 U.S. 519 (1966).

The utility requirement is not met where there is an absence of data supporting statements in a patent specification that set forth the desired results of the claimed invention. *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005). “If a patent claim fails to meet the utility requirement because it is not useful or operative, then it also fails to meet the how-to-use aspect of the enablement requirement.” *In re '318 Patent Litigation*, 583 F.3d at 1324 (internal quotation omitted); *see also In re Cortright*, 165 F.3d 1353, 1356 (Fed. Cir. 1999) (holding that claims that fail to disclose any “practical utility for the invention” are not enabled under 35 U.S.C. § 112(1)).

The claims of the Zeldis Patents are invalid under 35 USC § 101 because there is no indication in the disclosure beyond what was already obvious from the prior art that a person having ordinary skill in the art would have a reasonable expectation that the claimed methods would work for the purposes specified. The specifications of the Zeldis Patents are devoid of any data or showing that pomalidomide would be an effective treatment for multiple myeloma. The only clinical study in the Zeldis Patents concerning pomalidomide is a phase I pharmacokinetic study done by others, which does not provide data regarding efficacy. The only

other data in the specifications of the Zeldis Patents for pomalidomide are *in vitro* data for inhibition of TNF- α and for inhibition of myeloma cell proliferation (using MM.1S and Hs Sultan cells). *See, e.g.*, '262 patent, col. 31, lines 26-44. This data was already in the prior art. *See, e.g.*, D'Amato 2001 at 598-99; Muller. To the extent that this *in vitro* data in the prior art was insufficient to motivate the person of ordinary skill in the art to use pomalidomide in combination with dexamethasone to treat multiple myeloma and to provide that person of ordinary skill with a reasonable expectation of success, then the claims of the Zeldis Patents are invalid under 35 U.S.C. §§ 101 and 112, first paragraph (or (a) for the post-AIA claims of the '939 and '428 patents) because there is an absence of data demonstrating the asserted utility of the claimed methods.

G. Invalidity Under 35 U.S.C. §§ 102(f) & (g)(2)

All claims of the Zeldis Patents are invalid pursuant to at least 35 U.S.C. §§ 102(f) & (g)(2) at least because the listed inventor, Jerome B. Zeldis, did not invent himself the subject matter claimed in the Zeldis Patents, and/or the subject matter claimed in the Zeldis Patents was previously invented in this country by another inventor who had not abandoned, suppressed, or concealed it.

For example, Blood Vol. 121, No. 11 published Richardson et al. "Phase 1 study of pomalidomide MTD, safety, and efficacy in patients with refractory multiple myeloma who have received lenalidomide and bortezomib" on March 14, 2013 ("Richardson 2013"). Richardson 2013 reports on a clinical study (NCT00833833) that started in 2008 that administered the 4 mg maximum tolerated dose for oral pomalidomide on days 1 to 21 of a 28 day cycle, and used "a standard '3+3' design" for dose escalation." *Id.* at 1962. Jerome B. Zeldis is not listed as one of the authors on this publication. Yet, these authors claim through this publication to be the first to invent the claimed subject matter. The examples 6.5 in '262 patent, on the other hand, do not

have data to establish a maximum tolerated dose, nor do these examples include data from the administration to multiple myeloma patients. '262 patent at 33:1-38-14. Instead, the '262 patent includes only interim pharmacokinetic data. Further, Richardson 2013 identifies which authors “conceived and designed the study,” and none of these include Jerome B. Zeldis. Richardson 2013 at 1966. *See also* Schey I; Schey II; Schey III; Schey, S.A., et al., “Phase I Study of an Immunomodulatory Thalidomide Analog, CC-4047, in Relapsed or Refractory Multiple Myeloma,” *Journal of Clinical Oncology*, Vol. 22, No. 16 (Aug. 2004); Schey et al., “Pomalidomide therapy for myeloma,” *Expert Opin. Invest. Drugs* (2011) 20(5): 691- 700; Richardson, et al., Abstract O-12, 13th Int’l Myeloma Workshop, Paris, France (May 3-6, 2011). On information and belief, the authors of Richardson 2013 conceived of the claimed subject matter before Dr. Zeldis and communicated it to Dr. Zeldis; that communicated information was used to draft and prosecute the claims of the Zeldis Patents. Additionally, Jerome B. Zeldis submitted a declaration during the prosecution of the application that issued as the '569 patent, in which he states that he conceived of the invention claimed in that patent, which was lenalidomide, as shown by the clinical trial protocols for treating multiple myeloma with Revlimid (or lenalidomide). *See* Declaration by Jerome B. Zeldis dated May 30, 2006; Declaration by Jerome B. Zeldis dated October 26, 2005.

Moreover, pomalidomide for treatment of blood related cancers was conceived of and reduced to practice by Robert D’Amato and/or Robert D’Amato with others at The Children’s Medical Center Corporation, and not Jerome B. Zeldis. *See, e.g.*, U.S. Patent No. 5,712,291; D’Amato 1994; D’Amato 2001; WO 02/064083. *See also Celgene Corporation v. James E. Rogan and EntreMed, Inc.*, No. 1:02-CV-02277 (D.D.C. Nov. 19, 2002) (see, for example, Complaint filed on Nov. 19, 2002, briefing on Motion to Dismiss (e.g., Dkt. 5), briefing on

Motion for Preliminary Injunction (e.g., Dkt. 19)). In fact, Celgene licensed from EntreMed, Inc. the rights to lenalidomide and pomalidomide. *See* EntreMed Press Release (January 2, 2003). Thus, Jerome B. Zeldis did not invent the subject matter of the Zeldis Patents, and each of the asserted claims of the Zeldis Patents are thus invalid. Celgene has no standing to assert the Zeldis Patents since the true inventors of the claimed subject matter are not listed on the Zeldis Patent and did not assign their invention to Celgene. Defendants will likely have evidentiary support after a reasonable opportunity for further investigation or discovery that Celgene cannot correct the inventorship of the Zeldis Patents.

III. BASIS OF DEFENDANTS' CONTENTION THAT THE ASSERTED CLAIMS OF THE '427 PATENT ARE INVALID

Pursuant to L. Pat. R. 3.3 and 3.6(c), Defendants provide Plaintiff with the following written bases for its invalidity contentions with respect to the asserted claims of the '427 patent.

A. Priority Date

Even assuming that the '427 patent is entitled to the May 19, 2009 priority date, any reference published prior to May 19, 2009, qualifies as prior art to the '427 patent under 35 U.S.C. § 102(a), and any reference published prior to May 19, 2008, qualifies as prior art to the '427 patent under 35 U.S.C. § 102(b).

B. Prior Art That Anticipates or Renders Obvious Each Asserted Claim

Each and every asserted claim of the '427 patent is invalid as anticipated or rendered obvious by the prior art. The relevant prior art that would have been available to a person of ordinary skill in the art includes at least the following references, which are prior art to the '427 patent under at least 35 U.S.C. §§ 102(a), (b), (e), (f) and/or (g):

1. U.S. Patent Pub. 2007/0155791 ("the '791 publication"); [DEFS_POM_00012469-495]
2. U.S. Patent. No. 6,878,733 ("the '733 patent"); [DEFS_POM_00011290-425]

3. Schey, S.A., et al., *Phase I Study of an Immunomodulatory Thalidomide Analog, CC-4047, in Relapsed or Refractory Multiple Myeloma*, J. of Clinical Oncology, 22(16):3269-3276 (2004) (“Schey III”); [DEFS_POM_00013485-492]
4. U.S. Patent No. 5,635,517 (“the ’517 patent”); [DEFS_POM_00000175-185]
5. PCT Publication WO 02/43720 (“WO 02/43720” or “Hwu”); [DEFS_POM_00012413-467]
6. PCT Publication WO 98/03502 (“WO 98/03502”); [DEFS_POM_00012323-370]

Defendants reserve the right to rely on any combination of the above prior art in an obviousness defense, including to illustrate the background knowledge of a person of ordinary skill in the art, to demonstrate the motivation to combine prior art references, and to rebut any evidence of validity raised by Plaintiff. Brief summaries of the disclosures of some of the prior art references listed are set forth above under Section I.B. Defendants also identify and incorporate the combinations identified below and in the claim charts attached as Exhibit D.

C. Invalidity Based on Anticipation/Obviousness Under 35 U.S.C. §102/§103

All Asserted Claims of the ’427 patent are invalid as anticipated and obvious in view of the prior art. All dependent claims are anticipated or obvious over the prior art for the reasons discussed with respect to the independent and other dependent claims from which they dependent and such arguments are incorporated by reference.

1. Capsules containing pomalidomide, pregelatinized starch, sodium stearyl fumarate, and spray dried mannitol

All claims of the ’427 patent recite an oral dosage form in the form of a capsule which comprises: a specific weight of pomalidomide, pregelatinized starch, sodium stearyl fumarate, and spray dried mannitol.

A POSA in the field of pharmaceutical formulation would have found it obvious to select the well-known and widely-used excipients recited by the claims. For example, Remington’s Pharmaceutical Sciences, 18th ed. at 1658-1664 (“Remingtons,” [DEFS_POM_00013407-

453])¹³ provides that “powders for filling into hard gelatin capsules require the minimum of formulation efforts,” and teaches the use of excipients for capsules, including fillers (*e.g.* mannitol) and lubricants. As outlined in §II.C.7 above, such excipients, their functions and proportions in the formulation of oral dosage form capsules, including formulations of pomalidomide, were well-known before the priority date.

The '791 publication teaches oral dosage forms of pharmaceutical active ingredients, such as pomalidomide for the treatment of lupus. '791 publication ¶¶ [0002]-[0003]. The '791 publication teaches that the pharmaceutical compositions may be oral dosage forms, including oral capsules. *Id.* ¶ [0119]. The '791 publication teaches that lactose-free oral dosage forms comprise “excipients that are well known in the art” including fillers, such as pre-gelatinized starch. *Id.* ¶¶ [0112], [0124]. Additional fillers include mannitol. *Id.* ¶ [0124]. A POSA in the field of pharmaceutical formulation would be aware of the advantages of using the spray-dried form of mannitol, including flowability (*see, e.g.* Remingtons at 1646–1647). The '791 publication teaches that oral dosage forms may contain various lubricants, including magnesium stearate and silica gel. *Id.* ¶ [0127]. The '791 publication also teaches a pomalidomide dosage range of 0.5 mg to 2 mg per day. *Id.* at claim 30. The '791 publication also teaches that the daily dose of pomalidomide may be 0.1, 1, 2, 5, 10 or 25 mg per day. *Id.* at claim 29.

Thus, the '791 publication teaches capsules containing pomalidomide, pregelatinized starch and mannitol. Although '791 publication does not teach sodium stearyl fumarate in the amount recited in the claims, a POSA in the field of pharmaceutical formulation would have

¹³ This reference is incorporated by reference into the specification of the '427 patent at 5:9–18, which is deemed an admission of prior art status. *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1570, 7 U.S.P.Q.2d 1057 (Fed. Cir. 1988) (“A statement in a patent that something is in the prior art is binding on the applicant and patentee for determinations of anticipation and obviousness.”)

found it obvious to use sodium stearyl fumarate as it was a well-known lubricant. For example, it would have been obvious to use sodium stearyl fumarate in place of the magnesium stearate taught by the '791 publication. '791 publication ¶¶ [0112], [0145], [0154]-[0157], [0160]-[0163]. The '733 patent teaches that suitable lubricants for oral dosage forms include magnesium stearate and sodium stearyl fumarate (e.g., '733 patent at 150:66 – 151:3) and thus suggests that the two lubricants may be used similarly in oral dosage forms, and that these excipients can be interchangeable.

The '517 patent taught that pomalidomide can be prepared in “[o]ral dosage forms,” including capsules and tablets. *Id.* at 5:62-63. The '517 patent explained that the capsules can contain the compound and at least one pharmaceutically acceptable carrier, diluent or excipient. *Id.* at 6:4-6. Examples of suitable excipients include, inter alia, mannitol and starch. *Id.* at 6:15-24. *See also, e.g.,* '471 patent at 8:35-50 (disclosing that pharmaceutical compositions of pomalidomide may be in the form of a capsule and suitable excipients include mannitol and starch). In addition, Hwu disclosed compositions comprising pomalidomide for the treatment of cancer. Hwu at 19:12-13. Hwu further disclosed that these compositions could be administered in tablet or capsule form including excipients. *Id.* at 32:7, 32:29-33:1-5. Suitable excipients include fillers such as mannitol and pre-gelatinized starch. *Id.* at 36:7-10. WO 98/03502 disclosed that pharmaceutical compositions of pomalidomide could be in the form of a capsule and suitable excipients included mannitol and starch. WO 98/03502 at 12:16-13-4.

2. Capsules containing specific amounts of pomalidomide and excipients

The claims require specific amounts of pomalidomide and the recited excipients resulting in a specific cumulative weight. Specifically, claim 3 of the '427 requires 1 mg of pomalidomide, 70 mg of pregelatinized starch, 0.32 mg of sodium stearyl fumarate, and spray dried mannitol at a total weight of 125 mg. '427 patent at 32:12-19. Claim 5 requires 2 mg of

pomalidomide, 140 mg of pregelatinized starch, 0.64 mg of sodium stearyl fumarate, and spray dried mannitol at a total weight of 250 mg. '427 patent at 32:22-29. Claim 7 requires 3 mg of pomalidomide, 100.8 mg of pregelatinized starch, 0.45 mg of sodium stearyl fumarate, and spray dried mannitol at a total weight of 180 mg. '427 patent at 32:32-39. Claim 9 requires 4 mg of pomalidomide, 134.4 mg of pregelatinized starch, 0.6 mg of sodium stearyl fumarate, and spray dried mannitol at a total weight of 240 mg. '427 patent at 32:42-49.

The '791 publication teaches typical ranges or amounts of excipients and active ingredients used in oral dosage forms. For example, the '791 publication teaches dosage forms that include 0.1, 1, 2, or 5 mg of pomalidomide (§ [106]), and these amounts include or render obvious each of the claimed amounts. The '791 publication teaches that the amount of an active ingredient is a result-effective variable, and a person of ordinary skill would have found it obvious to select the claimed amounts, or combinations of these amounts, and further would have found it convenient to administer the entire pomalidomide dose per day in a single capsule.

Moreover, one of ordinary skill in the art would have understood that the amounts of excipients may be varied, as they would be recognized as result-effective variables, and would thus have varied the amounts of each of the excipients within known limits to optimize the properties of the formulation. Regarding the recited amounts of sodium stearyl fumarate, the '791 publication teaches the use of “lubricants” which are “typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms.” '791 publication ¶ [0127]. Each of the Asserted Claims of the '427 patent include lubricant sodium stearyl fumarate at an amount of less than 1% (w/w) of the “total weight of the composition.” Additionally, the '733 patent discloses capsule formulations comprising 0.25% (w/w) lubricant (*e.g.* Example 6, Table 9 at 251–252). Regarding mannitol and pregelatinized starch, the '791

publication teaches that fillers include mannitol and pregelatinized starch, and such fillers or binders are “typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.” ’791 publication ¶ [0124]. Each of the Asserted Claims include mannitol and pregelatinized starch which together comprise between 50 to 99% (w/w) of the “total weight of the composition.” Thus, one of ordinary skill in the art would have found the amounts of excipients to be obvious, having decided on an amount of pomalidomide. *See, e.g.* ’791 publication ¶ [0118] (“dosage forms contain predetermined amounts of active ingredients and can be prepared by methods of pharmacy well known to those skilled in the art”).

Thus, the prior art discloses ranges of weights that overlap with or include the claimed weights. *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004); *accord Lazare Kaplan Int’l, Inc. v. Photocscribe Techs., Inc.*, 628 F.3d 1359, 1380–81 (Fed. Cir. 2010); *see also Tyco Healthcare Grp. LP v. Mut. Pharm. Co.*, 642 F.3d 1370, 1372–73 (Fed. Cir. 2011). As such, the claimed weights are presumed obvious, and, as explained below, there is no evidence of unexpected results or criticality to rebut this prima facie case of obviousness.

Of further note, Schey III taught administration of pomalidomide to multiple myeloma patients in the range of 1 to 10 mg per day. Schey III at 2370. The 1 mg of pomalidomide required by claim 3 is the starting dose of the dose ranging study described by Schey. The 2 mg, 3 mg, and 4 mg of pomalidomide required in claims 5, 7, and 9, respectively, are each within the range disclosed in Schey III. *See also* Marriott 2002, Schey I, Schey II, & Section II.C.2.

Furthermore, determining the particular claimed weights of pomalidomide or the claimed excipients from the weights or ranges of weights disclosed in the prior art would have required no more than routine optimization of known variables. Optimization that flows from the normal

desire of scientists or artisans to improve upon what is already known is generally not patentable. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1366-67 (Fed. Cir. 2007).

3. Administration in a particular size of capsule

Claim 4 of the '427 patent further requires the dosage form to be administered in the form of a size 4 or larger capsule. Claims 6, 8 and 10 of the '427 patent further requires the dosage form to be administered in the form of a size 2 or larger capsule. '427 patent at 32:20-50. The '791 publication teaches the use of capsules (§ 0118). The '733 patent teaches capsules containing active ingredient, diluent, and lubricant in a size 0, 1, 2, 3 or 4 capsule shell. '733 patent at 252:64-67. Further, such capsule sizes were well-known and common in the industry. It would have been obvious to select from commercially available capsules and standard capsule sizes when creating a new dosage form. Thus, one of ordinary skill in the art would have found it obvious to select the corresponding shell size from those disclosed in the prior art, and, for example, based on the volume of the composition, capsules would have been preferred over other dosage forms (*see, e.g.* Remingtons at 1658–1664, describing the variation in capacity of capsules from 30 to 600 mg, and the practice of preparing sufficient volume in the capsule for manufacturing).

4. Objective indicia of nonobviousness

Defendants are unaware of any secondary considerations that weigh in favor of nonobviousness with respect to the asserted claims of the '427 patent. It is Celgene's burden to allege secondary considerations, and it has not done so in this litigation. Accordingly, Defendants have no secondary considerations to rebut and reserve their right to rebut any secondary considerations subsequently alleged by Celgene.

a. Unexpected Results

Defendants are not aware of any alleged unexpected results that weigh in favor of nonobviousness. As an initial matter, “[u]expected results that are probative of nonobviousness are those that are ‘different in kind and not merely in degree from the results of the prior art.’” *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013). In order for alleged unexpected results to be probative of nonobviousness, it must be proved that “there actually is a difference between the results obtained through the claimed invention and those of the prior art,” and that “the difference actually obtained would not have been expected by one skilled in the art at the time of invention.” *In re Freeman*, 474 F.2d 1318, 1324 (C.C.P.A. 1973) (citations omitted). Further, the Court must consider “what properties were expected.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007).

During prosecution of the ’390 application (which issued as the ’427 patent), Celgene alleged unexpected results of the claimed formulations. Celgene alleged that the claimed formulations exhibited unexpected stability, where other formulations failed. *See, e.g.*, Declaration of Anthony Tutino, June 14, 2014; Supplemental Amendment and Response, June 17, 2013, p. 8-9. Celgene relied on conjecture to suggest that the formulation disclosed in the ’791 publication would not be stable, but did not test the formulation. Celgene also relied on selected data to show that certain other formulations “present a compatibility problem, *i.e.*, were unstable after two weeks storage.” Declaration of Anthony Tutino, June 14, 2014 at ¶ 8. Celgene then presented long-term stability data to show that only one of the formulations was shown to be stable beyond 3 months. *Id.* at ¶¶ 9-10. However, any purported superior property must be unexpected to be considered as evidence of non-obviousness, and routine optimization within the ordinary skill of a POSA fails to meet this standard. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368, 82 U.S.P.Q.2d 1321, 1336 (Fed. Cir. 2007) (routine optimization to reach adequate

physicochemical characteristics, including stability, is not evidence of unexpected results). There is nothing in Mr. Tutino's declaration to suggest that the steps taken to optimize the formulation were anything less than routine, or that he did not expect to reach a stable formulation. Thus, Celgene has not shown evidence of any unexpected results tied to the claimed combination of excipients present in the claimed amounts.

A person having ordinary skill in the art would be able to vary the amounts of each of the claimed excipients, which were well-known, within known ranges to optimize the properties of the formulation and arrive at a stable formulation. Indeed, a stable formulation must have been created previously as used in Schey III, which administered capsules containing pomalidomide to multiple myeloma patients in the range of 1 to 10 mg per day. *See also* Marriott 2002, Schey I, Schey II, & Section II.C.2.

b. Commercial Success

Defendants are not aware of, and Celgene has not alleged, any commercial success that would weigh in favor of non-obviousness. . Furthermore, any purported success of Pomalyst® has no nexus to the subject matter claimed by the '427 patent. To be probative of nonobviousness, there must be a nexus between the commercial success and the novel features of the patented invention. *AstraZeneca LP v. Breath Ltd.*, 2015 WL 777460 (D.N.J. Feb. 13, 2015) (aff'd *AstraZeneca LP v. Breath Ltd.*, 603 Fed. Appx. 999 (Fed. Cir. 2015). "[I]f the commercial success is due to an unclaimed feature of the [invention], the commercial success is irrelevant." *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006). Likewise, "if the feature that creates the commercial success was known in the prior art, the success is not pertinent." *Id.* If a patentee can establish a nexus between commercial success and the patented invention, the challenger then bears the burden to show that the success was due to advertising or

other extraneous factors. *See, e.g., J.T. Eaton & Co. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997).

Any profits or revenue associated with sales of Pomalyst® do not demonstrate the non-obviousness of the claimed subject matter. For example, any such profits or revenue have no nexus to the claimed subject matter at least because these are attributable to other non-claimed features, such as Celgene's marketing activities, and/or to non-novel features of the '427 patent. Additionally, any sales of Pomalyst® alone are not indicative of the success of claimed elements that require administration with dexamethasone or other additional active agent. Furthermore, commercial success is not significantly probative if others in the field would have been deterred or inhibited from placing the product on the market by other forces, such as rights to exclude others from practicing the invention and/or impediments such as the burdens of regulatory approval (e.g. FDA approval). *Merck & Co., Inc. v. Teva Pharma. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005). The '427 patent is similar to and not patentably distinct from other prior patents claiming pomalidomide (e.g., the '471 patent and U.S. Patent Nos. 8,158,653, 6,476,052, 5,635,517). Any purported success is attributable to those patents and not to the Patents-in-Suit. Likewise, any purported success is not tied to the alleged novelty of the Patents-in-Suit, since, for example, it is attributable to the used of pomalidomide, which has already been claimed in other patents as stated above.

c. Skepticism

Defendants are not aware of, and Celgene has not alleged, any skepticism that would weigh in favor of non-obviousness.

d. Long-Felt but Unmet Need

Defendants are not aware of, and Celgene has not alleged, any long-felt but unmet need that would weigh in favor of non-obviousness.

e. Failure of Others

Defendants are not aware of, and Celgene has not alleged, any failure of others that would weigh in favor of non-obviousness.

f. Recognition in the Industry

Defendants are not aware of, and Celgene has not alleged, any recognition in the industry that would weigh in favor of non-obviousness.

g. Acquiescence

Defendants are not aware of, and Celgene has not alleged, any acquiescence to the validity of the '592 patent that would weigh in favor of non-obviousness.

h. Copying

Defendants are not aware of, and Celgene has not alleged, any copying that would weigh in favor of non-obviousness.

Secondary consideration evidence of copying in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval. *Bayer Schering Pharma AG v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013) (citing *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 377 Fed. Appx. 978, 983 (Fed.Cir.2010)); *see also Eli Lilly*, No. IP 02-0512, 2004 WL 1724632, at *38, n. 21 (stating “the very nature of a generic drug indicates that it is equivalent to the branded drug in certain significant respects.”); *Aventis*, No. 2:05-CV-421, 2006 WL 2008962, at *45 (asserting that “[the copying] rationale is considerably weakened . . . by the fact that there are various other reasons why an invention may

have been copied” (quoting MOY’S WALKER ON PATENTS, § 9:60 (4th ed. 2005)), rev’d on other grounds, 499 F.3d 1293 (Fed. Cir. 2007).

D. Invalidity Under 35 U.S.C. § 112¹⁴

1. Invalidity Under 35 U.S.C. § 112 for Indefiniteness

Defendants contend that the following claim limitations of the ’427 patent render the claims that include them, and all claims that depend from such claims, invalid:

- “An oral dosage form in the form of a capsule which weighs [x] mg” and “at an amount that brings the total weight of the composition to [x] mg” (claims 3–10); and
- “at an amount that provides [x] mg of 100% pure pomalidomide” (claims 3–10).
 - a. **“An oral dosage form in the form of a capsule which weighs [x] mg” and “at an amount that brings the total weight of the composition to [x] mg” (claims 3–10)**

Claims 3, 5, 7, and 9 of the ’427 patent require “[a]n oral dosage form in the form of a capsule which weighs” a specified weight. Claims 3, 5, 7, and 9 also recite that the dosage form comprises “at an amount that brings the total weight of the composition” to the same weight stated in the preamble of the claim. Claims 4, 6, 8, and 10 depend from these claims. ’427 patent at 32:12-52. These terms render the claims indefinite because a POSA would not know with reasonable certainty whether a dosage form falls within the scope of this claim, at least because the weights could be determined in various different ways (*e.g.* the “weight” could refer to the capsule fill alone, or for the capsule including its fill contents). Neither the specification nor the file history inform a POSA how the weight is calculated in order to determine whether a dosage form falls within the scope of these claims.

¹⁴ The application for the ’427 patent was filed May 19, 2010, and therefore pre-AIA 35 U.S.C. § 112 (applicable to applications filed before September 16, 2012) applies.

For example, the specification describes one embodiment of a dosage form comprising pomalidomide at an amount that provides about 1 mg of potency, 70 mg of pregelatinized starch, 0.32 mg of sodium stearyl fumarate, and spray dried mannitol “at an amount that brings the total weight of the dosage form” to 125 mg (’427 patent at 8:39–47, emphasis added). The specification refers to “dosage forms, such as capsules,” indicating that the capsule may be considered a “dosage form,” rather than the components of the capsule not including the capsule shell. Example 2 provides the formulation for a “1 mg strength pomalidomide capsule,” again reciting pomalidomide at an amount that provides about 1 mg of potency, 70 mg of Starch 1500, 0.32 mg of sodium stearyl fumarate (PRUV), and spray dried mannitol (Mannogem EZ) at an unspecified “remainder” weight, bringing the total weight of the “1 mg strength pomalidomide capsule” to 125 mg. ’427 patent at 29:1–13. The weight of the capsule shell is not listed in Example 2. It is therefore unclear whether the weight referred to in these claim limitations includes, for example, only the excipients and pomalidomide, or the capsule, excipients and pomalidomide together.

Accordingly, these terms do not allow a POSA to determine with reasonable certainty the metes and bounds of the claims, and thus the Asserted Claims of the ’427 patent are invalid.

b. “at an amount that provides [x] mg of 100% pure pomalidomide” (claims 3–10)

Claims 3, 5, 7, and 9 of the ’427 patent require pomalidomide “at an amount that provides [x] mg of 100% pure pomalidomide.” Claims 4, 6, 8, and 10 depend from these claims. ’427 patent at 32:12-52.

This term renders the claims indefinite because a POSA would not know with reasonable certainty whether a formulation falls within the scope of these claims, at least because the term can be understood to refer to the potency of pomalidomide as measured at different times during

the formulation process. Neither the specification nor the file history make clear how the amount and/or purity of pomalidomide is to be measured to determine whether a formulation falls within the scope of these claims.

For example, the specification provides:

In some embodiments, because it is typical to obtain pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, at a purity of less than 100%, the formulations and dosage forms provided herein may be defined as compositions, formulations, or dosage forms that comprise pomalidomide, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, or clathrate thereof, at an amount that provides the potency of a specified amount of 100% pure pomalidomide.

'427 patent at 7:26–34. The specification fails to define “pure pomalidomide.” For example, it is unclear whether the specified amount of “pure pomalidomide” must be present in the final dosage form prior to administration, or must be present when preparing the formulation before the excipients and pomalidomide are combined. Additionally, it is unclear whether the weight of pomalidomide accounts for varying molecular weight for “pharmaceutically acceptable salts” or “solvates” of pomalidomide, as recited by the claims, and whether such solvates or salts would be considered “pure” pomalidomide. For at least these reasons, a POSA would not be able to determine with reasonable certainty whether a given dosage form contains the specified amounts of “100% pure pomalidomide.”

Accordingly, this term does not allow a POSA to determine with reasonable certainty the metes and bounds of the claims, and thus the Asserted Claims of the '427 patent are invalid.

2. **Invalidity Under 35 U.S.C. § 112 for Lack of Written Description and/or Enablement**

The Asserted Claims of the '427 patent are invalid for lack of written description because the claimed subject matter is not adequately described by its disclosure, and because the specification fails to enable the full scope of the claims.

Claims 3, 5, 7, and 9 are directed to “oral dosage form[s]” comprising, *inter alia*, “pomalidomide, or a pharmaceutically acceptable salt or solvate thereof.” Claims 4, 6, 8, and 10 depend from these claims. ’427 patent at 32:12-52. A POSA reading the specification to the ’427 patent would not understand that the named inventors were in possession of an invention of dosage forms comprising pharmaceutically acceptable salts or solvates.

For example, the specification provides that “solvate” means “a compound provided herein or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces,” noting that where the solvent is water, the solvate is a hydrate. ’427 patent at 2:65–3:3. The specification also refers to “pharmaceutically acceptable salt(s)” as including at least 45 salts. ’427 patent at 2:39–64. These are mere examples. The plain and ordinary meaning of “a pharmaceutically acceptable salt or solvate thereof” may encompass many compounds, with varying physicochemical properties. The ’427 patent provides no working example or disclosure of formulation of a dosage form comprising a pomalidomide salt or solvate. During prosecution, the applicant submitted a Declaration of Dr. Tutino to the examiner in order to overcome an obviousness rejection, arguing that the stability of pomalidomide in formulations comprising various excipients and pomalidomide is not predictable.¹⁵ In allowing the claims, the examiner accepted these arguments.¹⁶ In light of these statements, a POSA would expect to require undue experimentation in order to determine which salt or solvate forms of pomalidomide would be compatible with the excipients recited by the claims. Even though a POSA would have found it obvious to use salt or solvate forms in the claimed dosage forms, the POSA would not have understood from the disclosures in the ’427

¹⁵ Arguments and Remarks Made in an Amendment, June 17, 2013, Ex. A at 2–4.

¹⁶ Notice of Allowability, May 5, 2015 at 4.

patent that the named inventors possessed an invention of dosage forms comprising salts or solvates, yet the claims are broad enough to encompass such forms.

For at least these reasons, the '427 patent does not provide adequate written description support for a person of ordinary skill in the art to reasonably conclude that the inventors had developed and were in possession of an oral dosage form comprised of pomalidomide salts or solvates described by the Asserted Claims, particularly those that would be useful in treating multiple myeloma. Further, the '427 patent does not enable a person of ordinary skill in the art to practice the full scope of the Asserted Claims without undue experimentation.

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WALSH PIZZI O'REILLY FALANGA LLP

/s/ Liza M. Walsh

Liza M. Walsh
Christine I. Gannon
Eleonore Ofosu-Antwi
One Riverfront Plaza
1037 Raymond Boulevard, Suite 600
Newark, NJ 07102
Tel.: (973) 757-1100

OF COUNSEL:

Jay P. Lefkowitz
Jeanna M. Wacker
KIRKLAND & ELLIS LLP
601 Lexington Avenue
New York, NY 10022
Tel.: (212) 446-4800
lefkowitz@kirkland.com
jeanna.wacker@kirkland.com

Kristen P.L. Reichenbach
KIRKLAND & ELLIS LLP
555 California Street
San Francisco, CA 94104
Tel.: (415) 439-1400
kristen.reichenbach@kirkland.com

*Attorneys for Defendant
Teva Pharmaceuticals USA, Inc.*

/s/ Roshan P. Shrestha

James E. Cecchi, Esq.
Melissa E. Flax, Esq.
Michael Cross, Esq.
CARELLA, BYRNE, CECCHI,
OLSTEIN, BRODY & AGNELLO, P.C.
5 Becker Farm Road
Roseland, NJ 07068-1739
973-994-1700
jcecchi@carellabyrne.com
mflax@carellabyrne.com
mcross@carellabyrne.com

Of Counsel:

Stephen R. Auten
Andrew M. Alul
Richard T. Ruzich
Brian P. Murray
Roshan P. Shrestha, Ph.D.
TAFT STETTINIUS & HOLLISTER LLP
111 East Wacker Drive
Suite 2800
Chicago, IL 60601
312-527-4000
sauten@taftlaw.com
aalul@taftlaw.com
rruzich@taftlaw.com
bmurray@taftlaw.com
rshrestha@taftlaw.com

*Attorneys for Defendants Hetero Labs Limited, Hetero
Labs Limited – Unit V, Hetero Drugs Limited, and Hetero
USA, Inc.*

/s/ Roshan P. Shrestha

Of Counsel:

Andrew M. Alul
Richard T. Ruzich
Stephen R. Auten
Brian P. Murray
Roshan P. Shrestha, Ph.D.
TAFT STETTINIUS & HOLLISTER LLP
111 East Wacker Drive
Suite 2800
Chicago, IL 60601
312-527-4000
aalul@taftlaw.com
rruzich@taftlaw.com
sauten@taftlaw.com
bmurray@taftlaw.com
rshrestha@taftlaw.com

James E. Cecchi, Esq.
Melissa E. Flax, Esq.
Michael Cross, Esq.
CARELLA, BYRNE, CECCHI,
OLSTEIN, BRODY & AGNELLO, P.C.
5 Becker Farm Road
Roseland, NJ 07068-1739
973-994-1700
jcecchi@carellabyrne.com
mflax@carellabyrne.com
mcross@carellabyrne.com

*Attorneys for Defendants
Apotex Inc. and Apotex Corp.*